PRIMARY BILIARY CIRRHOSIS AND PRIMARY SCLEROSING CHOLANGITIS MICAL S. CAMPBELL AND THOMAS FAUST pdf

1: Full text of "Cystic Fibrosis Related Liver Disease--Another Black Box in Hepatology."

Contents: Evaluation of the liver patient / Wolfram Goessling and Lawrence S. Friedman -- Cirrhosis and its complications / Jayanta Choudhury and Arun J. Sanyal -- Acute and chronic viral hepatitis / Barbara A. Piasecki -- Primary biliary cirrhosis and primary sclerosing cholangitis / Mical S. Campbell and Thomas Faust -- Autoimmune hepatitis.

The compositions further comprise one or more additional viable non-pathogenic or attenuated pathogenic microorganisms selected from the group consisting of Bacteroides, Eubacteria, Fusobacteria, Propionibacteria, Lactobacilli, anaerobic cocci, Ruminococcus, E. The present invention also provides pharmaceutical compositions suitable for the treatment of the same chronic diseases comprising viable non-pathogenic or attenuated pathogenic Escherichia coli, at least one strain of viable non-pathogenic or attenuated pathogenic Bacteroides and at least one strain of viable non-pathogenic or attenuated pathogenic microorganism. PQ , filed Jul. The aforementioned applications are expressly incorporated herein by reference in their entirety and for all purposes. TECHNICAL FIELD The present invention relates to pharmaceutical compositions suitable for the treatment of diseases in mammals, in particular to the treatment of chronic disorders associated with the presence of abnormal or an abnormal distribution of microflora in the gastrointestinal tract. The invention also relates to methods of treating such diseases. Pathophysiology of these disorders eludes logical explanation in spite of decades of research and millions of dollars of research funds. A common underlying factor shared by all these disorders observed by the present inventor is their onset or aggravation following some extraneous invading infection eg travellers diarrhoea. In all the disorders, a specific causal infection generally cannot be demonstrated due to our inability to detect infecting agents whose cultural characteristics are unknown to medical science. It is impractical to use long-term antibiotic therapy with its associated complications in such patients since cure is not obtained with its use. Some previous attempts have been made to alter the enteric microflora in order to eradicate such chronic infections. These measures nevertheless indicate that alteration of bacterial flora may effect dramatic clinical improvement in conditions characterised by chronic, resistant enterocolitic infection. However there remain many chronic disorders of uncertain aetiology or causation, which are resistant to cure by current therapeutic techniques. The use of probiotics in the human population has been largely confined to the inclusion in various foods of live organism of Lactobacilli and Bifidobacteria and less frequently Streptococcus faecalis or several strains of Escherichia coli. These organisms are thought to promote health via immune stimulation and reconstitution of what is presumed to be normal flora. Such usage stems back to the beliefs generated by Mechnikov in the early s. The use of probiotics to treat established infections in the gastrointestinal tract has been lesser but a growing part of the use of probiotics. Fungal agents such as Saccharomyces boulardii have been used to treat, albeit inefficiently, Clostridium difficile infection and Lactobacillus GG has also been used for this purpose Floch M. Probiotics and Dietary Fibre. J Clin Gastroenterol ; 27 2: Various patents have claimed the use of probiotics for narrow disease conditions including treatment of Clostridium difficile with a combination of Vancomycin and butyric acid bacteria U. Enterococcus faecium has been claimed to be useful in alleviating symptoms of Irritable Bowel Syndrome in humans U. Clostridium butyricum as a single agent has been claimed to be a biological intestinal antiseptic for treatment of bacterial food poisonings U. This patent also advocated the use of dried, reconstituted faeces or a synthetic mixture comprising Bacteroides sp. Such a replacement mixture has the dual ability of displacing pathogenic bacteria, frequently Clostridial in nature and also establishing a normal environment in which commensal bacteria can establish. Such a treatment permits long-term recovery both from gastrointestinal disorders and from systemic afflictions not hitherto considered to be caused by harmful enteric flora. Autism is a regressive disorder of childhood, affecting boys four times more often than girls. It has been observed that the onset of autism is often preceded by broad spectrum antibiotic use eg for recurrent ear infections. Antibiotic therapy is non-discriminatory in its action and apart from treating the ear infection

the microflora of the healthy gastrointestinal tract can be severely disrupted by such treatment. This creates an environment where vulnerability to opportunistic microorganism colonisation is heightened. Clostridium tetani is a widely distributed, spore forming anaerobe. Toxigenic strains of Clostridium tetani produce the extremely potent tetanus neurotoxin which is known to enter the central nervous system from the intestinal tract via the vagus nerve Hensel B et al. Naunyn Schmeidebergs Arch Pharmocol ; Bolte Med Hypotheses ; Others have also raised the possibility of clostridia in general as a cause of disease Borriello S P. Clin Infect Dis ; Suppl 2: All children in the trial had had antecedent broad-spectrum antibiotic exposure, followed by chronic persistent diarrhoea and then onset of autistic features. Although significant post-treatment improvement was noted, all children eventually regressed towards baseline. It is on the background of these known facts and later the results of trials of treatment, that the present invention was formulated. However, not only did their IBS improve dramatically but also their autistic features progressively regressed. Continuing improvement was observed to occur over 12 months of treatment. The inclusion within this specification of reference to published documents is not to be taken to be an admission that any one or more of those documents, nor the disclosure of any one or more of those documents, is part of the common general knowledge. Objects of the Invention.

PRIMARY BILIARY CIRRHOSIS AND PRIMARY SCLEROSING CHOLANGITIS MICAL S. CAMPBELL AND THOMAS FAUST pdf

2: Bile acids as endogenous etiologic agents in gastrointestinal cancer

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis Mical S. Campbell, MD and Thomas Faust, MD chapter 4 IntroductIon Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease that predomi-.

Due to improved medical care, life expectancy in patients with cystic fibrosis CF has veritably improved over the last decades. Importantly, cystic fibrosis related liver disease CFLD has become one of the leading causes of morbidity and mortality in CF patients. However, CFLD might be largely underdiagnosed and diagnostic criteria need to be refined. The underlying pathomechanisms are largely unknown, and treatment strategies with proven efficacy are lacking. This review focuses on current invasive and non-invasive diagnostic standards, the current knowledge on the pathophysiology of CFLD, treatment strategies, and possible future developments. Introduction Cystic fibrosis CF is the most frequent fatal autosomal recessive disorder in Caucasians. It results from mutations within the cystic fibrosis transmembrane conductance regulator CFTR comprising more than known mutations [1]. CFTR encodes for a protein that is found in epithelial cells of lungs, sweat glands, pancreas, intestine and liver. Thereby, it maintains an alkaline pH and dilutes fluid secretions [4]. Defects of CFTR lead to dehydration of secretions and hyperviscous mucus causing a multisystem disease with major affection of the respiratory, gastrointestinal, and hepatobiliary tract. Albeit lung disease remains the main cause of morbidity and mortality, the changing demographics of CF necessitate an increased focus also on other organ manifestations. CF-related liver disease CFLD was recently shown to be an independent risk factor for mortality and lung transplantation, and has become one of the leading causes of death among patients with CF [6]. Clinical Presentation of CFLD The absence of functioning CFTR may lead to cholestatic liver disease with reduced bile flow and focal biliary obstruction causing periductal inflammation, proliferation and finally periportal fibrosis. The morphological findings are diverse and comprise liver alterations ranging from steatosis to primary sclerosing cholangitis PSC â€”like bile duct lesions, cholestasis, biliary cirrhosis, and alterations of the gall bladder i. However, our practice is to perform annual ultrasound of the abdomen in all patients with CF, as ultrasound is non-invasive, cost-effective and highly valuable for the diagnosis of hepatic steatosis, cirrhosis and complications of portal hypertension such as ascites and splenomegaly. Several studies have demonstrated that clinical evaluation, serum liver enzymes and ultrasound are imprecise for detecting the presence and predicting the progression of liver disease [10 , 11 , 12 , 13]. Thus, for patients in whom diagnosis is still inconclusive after standard work-up see above including exclusion of other causes of liver disease viral, autoimmune, metabolic, genetic percutaneous liver biopsy representing the diagnostic gold standard, can be performed [8]. Although liver biopsy is invasive, complication rates after liver biopsy in CF patients seem to be low even when dual pass liver biopsies are performed no bleeding, hospital admission, prolonged pain or surgery [9 , 13]. However, a substantial sampling error due to typically focally distributed lesions in CFLD can complicate diagnostic algorithms. Since all established diagnostic measures cannot reliably preclude CF related liver involvement, there is an urgent clinical need for advanced diagnostic tools. Minimally- and non-invasive methods for assessment of liver fibrosis have recently become a focus of interest in the diagnosis and management of CFLD. Serum Parameters and Emerging Biomarkers Serum markers offer an attractive and cost-effective approach. The impact of abnormalities of serum liver enzymes, however, is limited in screening for CFLD. Elevation of transaminases aspartate amino transferase AST , alanine amino transferase ALT or cholestasis parameters alkaline phosphatase AP , gamma glutamyl transferase GGT are frequently mild or intermittently present, sensitivity and specificity are low and abnormalities usually do not correlate with histological findings. Liver enzymes may be even normal although multilobular biliary cirrhosis is present [8]. However, serum markers of liver fibrosis may be useful for early detection of patients with CFLD and identify patients at risk for progression of liver disease. In a case control study, Pereira et al. Nevertheless, validation studies are lacking. Their sensitivity was further increased by combinational use of transient elastography TE sensitivity of TE and

endoglin: ARFI imaging combines conventional ultrasonography with evaluation of local liver stiffness. Regions of evaluation are chosen by ultrasound, allowing avoidance of anatomic obstacles [19 , 20]. Shear Wave Velocity increased progressively from patients with no evidence of CFLD to patients with CFLD with no evidence of portal hypertension to those with signs of portal hypertension [21]. Elastography values in CFLD cirrhosis differed from cut-off values in patients with alcoholic cirrhosis or those reported in viral hepatitis induced cirrhosis, strengthening the assumption, that elastography values depend on the etiology of liver disease [22]. MRI technology can be used both for measurement of liver stiffness by Magnetic Resonance Elastography; MRE; no data available in CF , and evaluation of liver parenchyma and bile duct alterations [27], but is associated with substantially higher costs and examination times than TE or ARFI. In a study from in 27 adult CF patients 1. As the hepatic manifestation of the metabolic syndrome, NAFLD is typically encountered in individuals with insulin resistance. Although steatosis in CF does not seem to be related to a CFTR secretory defect, but has been associated with selective nutritional deficiencies and altered phospholipid metabolism, its relevance as a risk factor for the development of steatohepatitis and progression to cirrhosis in CF patients is unclear. Primary Sclerosing Cholangitis Primary sclerosing cholangitis PSC is a chronic progressive cholestatic disorder of unknown etiology characterized by inflammatory bile duct alterations resembling those seen in CF [32]. Mutations in CFTR, which in general is highly expressed on biliary epithelial cells [33], have been detected in PSC patients [34 , 35], although other studies have revealed discordant results [36]. Both CF and PSC with IBD are associated with an extremely high rate of colorectal cancer [37 , 39] adding to the similarities between these two disease entities. However, in contrast to CF, which only affects the intrahepatic bile ducts, PSC can involve the intrahepatic, extrahepatic bile ducts or both and leads to concentric obliterative fibrosis with bile duct strictures leading to disruption of biliary secretion and finally biliary cirrhosis [37 , 40]. Secondary Sclerosing Cholangitis Secondary sclerosing cholangitis SSC comprises a group of cholangiopathies which are morphologically similar to PSC but originate from a known pathological process, suggesting that widely different insults may give rise to a similar pattern of biliary disease [41]. Thus, the diagnosis of PSC requires the exclusion of secondary causes of sclerosing cholangitis and careful history-taking is key. Differentiating between PSC and SSC or the various causes of SSC and SSC can be particularly difficult, since common causes of SSC such as previous bile duct surgery, cholangiolithiasis, recurrent pancreatitis, recurrent infectious cholangitis, portal biliopathy bile duct and gallbladder wall anomalies seen in patients with portal hypertension , or ischemia-induced bile duct lesions, also called ischemic cholangitis [42] e. Noteworthy, IgG4-associated cholangitis IAC , another cause of SSC, is a steroid-responsive cholangiopathy, which is biochemically and cholangiographically indistinguishable from PSC, but is often associated with autoimmune pancreatitis and other fibrosing conditions e. It is characterized by elevated IgG4-levels and infiltration of IgG4 positive plasma cells in bile ducts and liver tissue. Unlike PSC, it mainly affects elder individuals and has a good long-term prognosis [43 , 44]. It is very likely, that a combination of CFTR genotype, individual susceptibility to environmental factors and the bi-directional influence of affected organ systems in combination lead to the development and progression of CFLD, rather than one single hit [45 , 46]. It is to mention, that history of meconium ileus, as well as exocrine pancreatic insufficiency and younger age at diagnosis, all associated with more severe CFTR mutation classes, have been identified as risk factors for the development of CFLD [47 , 48]. The resulting ductular biliary obstruction and portal inflammation may first cause a focal, but later multilobular fibrosis and cirrhosis. A recent case report refers to an infant with CF presenting with neonatal cholestasis mimicking biliary atresia, in whom a new CFTR mutation c. Impact of Lipid and Glucose Homeostasis Low BMI, abnormal nutritional parameters, growth failure associated with exocrine pancreatic insufficiency pancreatic atrophy with lack or reduction of digestive enzyme secretion leading to fat malabsorption , and CF-related diabetes CFRD have been linked to the development of CFLD, all conditions that might be related to dyslipidemia normal to low total cholesterol, low high density lipoprotein HDL , low density lipoprotein LDL , high triglycerides. Nevertheless, very little is known about alterations in lipid homeostasis in CF prior to and

after lung transplantation. Additionally, BA composition is altered in CF patients, showing higher levels of the primary BA cholic acid and chenodeoxycholic acid. Serum cholic acid levels were associated with hepatic fibrosis, inflammation and limiting plate disruption [58]. In a study in CF patients without CFLD, total fecal BA levels were markedly increased compared to healthy controls showing a selective malabsorption of cholic acid [59]. However, studies investigating the mechanisms at the basis of BA malabsorption and altered enterohepatic BA circulation in CF patients are lacking. Intestinal FGF19 functions as an enterokine that signals the presence of BA in the intestine to the liver. This signal transduced by fibroblast growth factor receptor FGFR 4 and the involved protein cascade suppresses CYP7A1, the rate limiting enzyme of BA synthesis in the liver [61 , 62]. Impaired FXR signaling is associated with increased hepatocellular damage upon bile acid challenge [63]. Of note, FGF19 was shown to be ectopically expressed in livers of cholestatic patients, representing an adaptive response reducing disease progression [64]. Selective activation of FXR in the intestine protects mice against cholestasis by activation of FGF15 mouse ortholog of FGF19 via a negative feedback loop to hepatic bile acid synthesis [65]. Under the condition of biliary obstruction mice lacking FXR have induced intestinal inflammation and bacterial overgrowth [65]. Recently, Ho et al.

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3: USB2 - Probiotic recolonisation therapy - Google Patents

Mical S. Campbell, Gary R. Lichtenstein, Andrew D. Rhim, Michael Pazianas and Thomas Faust, Severity of liver disease does not predict osteopenia or low bone mineral density in primary sclerosing cholangitis, Liver International, 25, 2, (), ().

Arnold,1 Maxwell Farrell,1 and Mark S. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Fair allocation of organs to candidates listed for transplantation is fundamental to organ-donation policies. Processes leading to listing decisions are neither regulated nor understood. We explored whether patient characteristics affected timeliness of listing using population-based data on , adults hospitalized with liver-related disease in Pennsylvania. We linked hospitalizations to other secondary data and found 3, listed for transplants, 1, received transplants, and 57, died. Using competing-risks models, we found few overall differences by sex, but both black patients and those insured by Medicare and Medicaid combined waited longer before being listed. Patients with combined Medicare and Medicaid insurance, as well as those with Medicaid alone, were also more likely to die without ever being listed. The early time period from diagnosis to listing for liver transplantation reveals unwanted variation related to demographics that jeopardizes overall fairness of organ allocation and needs to be further explored. Introduction Historically, in cases where empirical data have shown systematic differences in waiting times or in the chances of Because the demand for transplant services has always receiving a transplant, UNOS has changed its policies to exceeded the supply of donor organs, the transplant com- improve organ allocation procedures. Examples of changes munity as well as policymakers have long recognized the include the institution of less stringent HLA-matching need to ensure that the organ allocation system is efficient requirements for renal transplantation [9], the adoption of and equitable [1â€”6]. The United Network for Organ Sharing the final rule [6], and the use of the model of end-stage UNOS , which oversees waitlisting and allocation guidelines liver disease MELD scoring system for liver transplantation in the United States, indicates that access to organs will not [10, 11]. But of Medicine, the transplant process involves numerous steps for other types of solid organ transplantation, including and inequities can take place anywhere along the way [8]. Based on our previous work [17], incidence , disease progression natural history , disease we classified patients in terms of 9 major categories of diagnosis, referral, and evaluation by a transplant center, disease: We previously reported that cancer, primary biliary cirrhosis, other chronic liver disease, demographics were important in determining the likelihood and acute liver failure. This left us with a cohort of , transplantation once they were listed [15]. This initial patients with liver disease from hospitals that had analysis evaluated only whether or not patients progressed been newly diagnosed between and We linked to specific stages of the transplantation process; because of the index hospitalization records of these patients to the missing data, it did not address matters related to timing and following: Specifically, we Pittsburgh Medical Center, and the VA Pittsburgh Healthcare examined waiting times experienced by subsets of patients System , the listing, allocation, and transplant data from during 2 time periods. This allowed us to deter- of a transplant an interval in which there is oversight. In each case, there were 3 waiting list. Methods The unit of analysis was the patient not the registration. Although the data were deidentified by the honest broker, 2. Data Sources and Data Management. Our conceptual multiple listings could be identified and reconciled using framework, data sources, and patient cohort have been a pseudoidentifier for patients. We combined the dates described previously [15]. We assumed that most individuals earliest definitive outcome i. Second, discharges, and the accuracy of the data has been validated for patients with multiple listings, we took the earliest listing against chart reviews [16]. Both of these conventions minimize early The PHC4 listed participating hospitals statewide waiting time from diagnosis until listing and maximize later during the study period. It provided us with data for all waiting times from listing to transplant, serving to bias patients with liver-related stays

between and We protected age, had commercial health insurance only, had a diagnosis patient confidentiality by having the PHC4 serve as an honest of viral hepatitis, alcoholic liver disease, or autoimmune broker to link records across data sources and provide our disorder, and had a moderate or severe level of illness. Because of the large sample size, between-group differences were statistically significant for all covariates. In general, however, differences between the first and second groups 2. To characterize patients in terms of full cohort and listed patients were larger than differences sociodemographic and clinical data, stage of the allocation between the second and third groups listed patients and process diagnosis, listing, and receipt of a transplant , transplant recipients. Of the , adults in our final cohort of patients To compare the characteristics of subsets of patients with liver-transplant potential, 3, 2. Of these 3, patients, 1, multivariable survival models that included the following Among transplant recipients, uninsured, and unknown based on the index hospitaliza- A total of 57, patients Given our focus on state- 3. Because waiting times are cen- level data, there was no variation in terms of geographic sored for patients who do not progress to the next stage of the region, but we did include location of transplant center process e. We included year of percentage of patients who progressed to the next stage of the index hospitalization and also tested for interaction variables transplantation process within specific time intervals, first e. Similarly, we looked at differences in later waiting top panel. During the same period, In the received transplants at these same intervals. In both cases, we stratified results, women diagnosed with liver disease were controlled for the competing risk of death. In terms of insurance waiting list. Black patients showed the 3. Results same pattern, with fewer transplants and more deaths than white patients. Both the Medicare patients and the uninsured Table 1 shows data for 3 groupsâ€”the full cohort, the subset patients including self-pay patients were listed at higher- of patients listed for transplantation, and the final subset than-average rates, but the Medicare patients had higher- of patients who received transplantsâ€”stratified by sociode- than-average risks of death while the uninsured patients had mographic and clinical characteristics. In all 3 groups, the lower-than-average risks of death. Full cohort of patients Patients who were listed for a transplant Patients who received a transplant Characteristic, no. Not applicable for patients at the diagnosis stage. The main effect of insurance The information is analogous to that presented in Table 2 for Journal of Transplantation 5 Table 2: Unadjusted time to listing and time to transplantation, controlling for competing risk of death. Of note, in competing risk models, of the competing risk graphs right-hand side in Figure 1 if the longest noncensored followup time in the observed through 3; this artifact is similar to the way in which Kaplan- data set coincides with a patient death, then the estimated Meier graphs show no survivors at the end of the followup cumulative incidence function for death i. Diagnosis-specific interaction results for gender are risk converges to 1. This is the case for all provided in Figure 4. Regressions in the multivariable competing risks model with interaction terms. Listing Death before listing 0. Gender-related results in the adjusted competing risks model. Journal of Transplantation 9 Listing Death before listing 1 0. However, the overall effect of gender on early waiting time was slightly different when the interactions between 3. The interaction terms indicate that only black the early period than men overall, as shown in Figure 1 a. Insurance-based results in the adjusted competing risks model. After listing, there was no variation related to insurance status: Time to listing was similar for transplant were similar for all payer groups Figures 3 a and most insurance status groups Figures 3 a and 3 b. Journal of Transplantation 11 Listing Death before listing 1 0. Discussion period, in terms of both the likelihood of being listed for transplant and the likelihood of death without ever being Our analyses of a statewide population-based data set for listed. These patterns may be indicative of disease waiting times before being listed for transplant as well progression when patients present with symptoms in this as risk of death. Although the overall experiences were case, when patients are hospitalized , but our analyses did similar for men and women before listing, there was sub- adjust for disease severity at the time of diagnosis. Once patients are placed on the transplant waiting list, Black patients were less likely to be listed for transplant gender appeared more significant as women waited longer to upon diagnosis. Insurance status also mattered in the early receive a transplant; black patients were more likely to die 12 Journal of Transplantation on the waiting list without a transplant, but insurance status Center

for Research Resources NCRR and the National played no role in later waiting time differences. Data used in this paper were tioning. Second, although the study linked UNOS. The PHC4 is an independent state agency that has information from 5 participating transplant centers, this provided data in an effort to further its missions of educating information varied across centers in terms of format, detail, the public and containing health care costs in Pennsylvania. As a result, we could only explore The PHC4, its agents, and staff have made no representation, disparities for 2 periods diagnosis to listing and then listing guarantee, or warranty express or implied that the data to transplant. A more comprehensive analysis of early dis- provided are error-free or that the use of the data will avoid parities requires standardizing the data that are collected at difference of opinion or interpretation, and they bear no these earlier transitions in the transplantation process prior responsibility or liability for the results of the analysis, which to listing diagnosis to referral, referral to evaluation, and are solely the opinion of the authors. UNOS is the contractor evaluation to listing. Third, insurance status was based on for the Organ Procurement and Transplantation Network the index hospitalization only; any potential changes in payer OPTN. The interpretation and reporting of UNOS data are information were not observed. Fourth, the study period the responsibility of the authors and in no way should be seen predates the MELD scoring system, though it is worth noting as an official policy of or interpretation by the OPTN or the that our main finding i. The authors of the paper have no conflict of status are associated with variability in early waiting times interests, including financial interests and relationships and refers to stages of the organ allocation process that are affiliations relevant to the subject of the paper. Abbreviations To our knowledge, our study is the first population- DRG: Medical illness severity grouping system services. Previously, we reported differences in the overall MELD: Model for end-stage liver disease likelihood of moving through the allocation and transplant PHC4: Pennsylvania Health Care Cost process [15]. The results of the study reported here confirm Containment Council those earlier findings and provide strong evidence that UNOS: United Network for Organ Sharing. With the persistent gap between demand for transplant Acknowledgments services and supply of available donor organs, much effort The authors acknowledge assistance from the staff at Penn- by policymakers and the transplant community is devoted sylvania Health Care Cost Containment Council, Maureen to ensuring the fairness of the transplant system. Still lacking, Ignazio R. Marino Jefferson Medical College, Thomas Jef- however, are centralized data sources to accurately measure ferson University , Cosme Manzarbeitia Thomas Jefferson the denominator populationâ€”that is, the population of University , Joe Donaldson Starzl Transplant Institute , and all individuals who have end-stage liver disease and are D. Renae Geraci University of Pittsburgh. Only with these data can researchers and policymakers measure the true demand for liver-transplant services, assess the fairness of the process, References and optimize the allocation of available donor organs. Support and Disclaimers [2] E. UL1 RR from the National 20, no. Journal of Transplantation 13 [4] P.

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4: HELEN TE | Profiles RNS

Thomas W. Faust, Recurrent primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis after transplantation, Liver Transplantation, 7, 11B, (ss), (). Wiley Online Library.

Abstract The question of whether health care inequities occur before patients with end-stage liver disease ESLD are waitlisted for transplantation has not previously been assessed. To determine the impact of gender, race and insurance on access to transplantation, we linked Pennsylvania sources of data regarding adult patients discharged from nongovernmental hospitals from to Using multinomial logistic regressions, we estimated probabilities that patients would undergo transplant evaluation, transplant waitlisting and transplantation itself. Of the patients in the study, 3. Of those evaluated, Of those waitlisted, Overall, 57 Differences were more pronounced for early stages evaluation and listing than for the transplantation stage in which national oversight and review occur. For early management and treatment decisions of patients with ESLD to be better understood, more comprehensive data concerning referral and listing practices are needed. These changes, however, can only have minimal impact, as the allocation of organs is simply the last step in transplantation, and potential barriers can be encountered at the diagnostic, referral or listing stages as well. Indeed, as Alexander and Sehgal observed in their study of end-stage renal disease, gender- and race-based barriers to care are found at all stages of management, from diagnosis of end-organ disease through the actual receipt of an organ 8. No similar registry exists for patients with liver disease. However, the UNOS waitlist includes only those individuals who were listed by transplant centers 10 , and it fails to account for potential inequities associated with diagnosis, referral or evaluated-but-not-listed decisions. Previous evaluation of the early stages of the process leading to liver transplantation has been survey based or limited to descriptions of center-specific practices 12 â€” A survey conducted by the American Society of Transplant Physicians reported on practice variation across centers, including both patient factors e. The authors reported that although blacks were referred to their center less often than appropriate given their prevalence of liver disease and were sicker at referral than whites, once evaluated, blacks and whites were equally likely to be listed for transplantation, to receive a transplant and had similar 1-and 3-year posttransplant survival rates. More recently, Julapalli et al. To our knowledge, the only population-based study of early access to transplantation services used discharge data for the state of North Carolina to estimate the prevalence of ESLD and the covariates associated with the likelihood of liver transplantation. Although several nonmedical factors e. This study follows patients with liver disease who might potentially need a liver transplant in the future, allowing us to examine the early barriers to access and the impact of sociodemographic factors i. We compare sociodemographics observed prior to listing with those observed after listing, as a way of assessing whether later stages provide an accurate picture in describing the overall equity of the current liver transplantation process. The main hypothesis of this study is that gender, race and insurance status affect early access to liver transplantation services namely, referral to transplant centers and listing by transplant centers differently than they affect access after patients are placed on the transplant waiting list. Model development and data collection We defined six stages that a patient with liver disease must pass through prior to transplantation Figure 1:

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5: è‚•ç—…ä¸´åºŠæŒ‡å¯¼The clinicianâ€™s guide to liver disease() - é•“å®¢å·´å·´

Evaluation of the liver patient / Wolfram Goessling and Lawrence S. Friedman --Cirrhosis and its complications / Jayanta Choudhury and Arun J. Sanyal --Acute and chronic viral hepatitis / Barbara A. Piasecki --Primary biliary cirrhosis and primary sclerosing cholangitis / Mical S. Campbell and Thomas Faust --Autoimmune hepatitis / Stanley.

July 29, First decision: September 18, Revised: November 13, Article in press: December 1, Published online: March 9, Abstract Hepatocellular carcinoma HCC is the most frequent form of liver cancer and the third most common cause of cancer-related death in the world. The main risk factor worldwide for this type of malignancy is chronic hepatitis caused by hepatitis B virus and hepatitis C virus infections. Advances in early detection and treatment have improved life expectancy of patients with HCC. However, this disorder remains as a disease with poor prognosis. Additionally, HCC is particularly difficult to treat because of its high recurrence rate, and its resistance to conventional chemotherapy is due, among other mechanisms, to several members of the ATP-Binding Cassette protein family involved in drug transport being overexpressed. Fortunately, there is evidence that these patients may benefit from alternative molecular-targeted therapies. This manuscript intends to provide further insight into the etiology and molecular mechanisms related to HCC development and the latest therapeutic approaches to treat this malignancy. The development of effective delivery systems of antitumor drugs able to target the liver parenchyma is also assessed. Finally, the prospects in the development of more efficient drug therapies to overcome multidrug resistance are also examined. Hepatocellular carcinoma , Therapy , Multidrug resistance , Drug delivery systems , Liver targeting Core tip: Hepatocellular carcinoma HCC is the most frequent malignancy of the liver. Despite the advances in early detection and treatment, this disorder still has a poor prognosis. This manuscript reviews the ongoing knowledge regarding the etiology and molecular mechanisms implicated in HCC development and the therapeutic strategies for the management of this malignancy. Finally, the development of effective delivery systems of antitumor drugs able to target the liver parenchyma as well as the prospects in the development of a more efficient drug therapy to overcome multidrug resistance are also examined. Hepatocellular carcinoma and multidrug resistance: Past, present and new challenges for therapy improvement. Its clinical course is aggressive, while frequent recurrence and metastasis are often associated with this malignancy. Other common causes leading to the development of this malignancy are: Several potentially curative or palliative approaches to the treatment of HCC are available. The surgical approaches that are most commonly chosen are: However, preserved or adequate liver function is an essential criterion for surgical resection. In this regard, this surgical approach is not a feasible option for HCC patients[10] when the tumor is at an advanced stage, or is located in close proximity to important hepatic vessels within the liver preventing a negative-margin resection, or when there are tumors at multiple sites or there is inadequate remaining hepatic function. Orthotopic liver transplantation is considered to be the only curative solution for HCC that cannot be surgically removed. Candidates for this procedure are those patients having solitary HCCs of less than 5 cm in size or up to three nodules, each smaller than 3 cm[12 , 13]. Nevertheless, this procedure has limited availability due to the great difficulty in finding organ donors[10]. Non-surgical therapeutic approaches for HCC such as radiofrequency ablation RFA , percutaneous ethanol injection PEI , transarterial embolization TAE and transarterial chemoembolization TACE are other therapeutic tools used to substitute first-line procedures; however, the probable course of the disease for the patients undergoing such procedures is still bleak. A research study confirms that so far there are no adjuvant therapeutic postoperative regimens to successfully treat HCC. A clinical investigation indicates that none of the adjuvant therapies is particularly effective in the treatment of HCC after surgery[16]. Systemic chemotherapy with doxorubicin, immunotherapy using interferon and hormonal therapy with tamoxifen, on the other hand, yielded poor results, with no significant survival benefits compared with symptomatic management[17 - 19]. One important limitation in the chemotherapy for HCC is the emergence of multidrug resistance MDR to conventional anti-tumoral agents[20

]. This phenotype is commonly related to cancer cells that are able to overexpress drug transporter proteins belonging to the ATP-binding cassette ABC superfamily of proteins that move drugs out of cells, such as P-glycoprotein P-gp , the multidrug resistance-associated proteins MRPs and the breast cancer resistance protein BCRP [21]. Additionally, current anti-tumoral drugs used in HCC treatment, also promote significant toxicities in other non-target organs affecting patient compliance and adherence to these therapeutic regimens[22]. Enhanced delivery[23] of these commercially available anti-cancer agents to liver parenchyma may provide an opportunity to selectively improve the efficacy of the current therapies and simultaneously reduce the adverse effects that often lead to treatment failure. Up to now, no succesful systemic chemotherapy for patients with advanced and unresectable HCC is available. Unfortunately, this promising treatment has demonstrated limited survival benefits with very low response rates[24 , 25]. Therefore, new approaches are urgently needed for: In this analysis we review the available information regarding the latest pharmacotherapy options for the treatment of patients suffering from advanced HCC, including molecular targeting agents. In these advanced stages, systemic treatments are commonly used; however, they are also minimally effective, have severe side effects, develop high drug resistance, and most importantly, patient survival is not improved. HCC is rarely amenable to radiotherapy, leaving this disease with no effective therapeutic options and a very poor prognosis[27]. Through better understanding the molecular basis of hepatocarcinogenesis e. Surgical therapies At present, surgical resection and orthotopic liver transplantation offer the only chance for long-term cure of patients suffering from HCC. Surgical resection is an effective treatment for those patients with HCC that is not associated with liver cirrhosis or in patients whose hepatic function is well compensated. Thus, both tumor extent and hepatic function must be evaluated pre-operatively to avoid hepatic failure following resection, which is usually a fatal condition possibly requiring urgent liver transplantation. Nevertheless, there is a limitation as to the use of this procedure, since the shortage of human donors is an unfortunate event these days[10]. Due to the strictness of Milan criteria regarding transplantation and the restrictions in finding available donors, scientists are now devoted to exploring other therapies for managing the disease in order to provide a solution for the disadvantages arising from transplantation or surgical resection[30]. Non-surgical therapies Locoregional therapies: Percutaneous ablation PA is now the first alternative treatment when resection or orthotopic liver transplantation has been ruled out in patients suffering from early-stage HCC. PA can be thermal or chemical. The thermal ablation procedure destroys cancer cells by cryoablation or by heat using lasers, high intensity focused ultrasound, microwaves or radiotherapy. Chemical ablation consists on cancer cells destruction by injecting chemicals - e. The ablative method as a treatment of choice will be based on the size of the tumor. RFA radiofrequency ablation is another ablative procedure initially outlined by Rossi et al[33], in , and since then, it has become the favorite form of ablation for small tumors. When comparing RFA with PEI, the former showed to be better in relapse prevention and in improving tumor necrosis[30]. However, surgical resection is so far very superior to PA techniques. TAE is another locoregional palliative treatment option in cases where surgical resection or other forms of treatment with curative potential are not advised for specific HCC tumors. The hepatic artery is responsible for the supply of blood to the tumor; therefore, the obstruction caused by TAE produces extended tumor necrosis as a result of ischemia, thus providing the rationale for its wide use in patients with HCC[34]. When this procedure is performed in combination with chemotherapeutic agents such as doxorubicin and cisplatin, usually mixed with lipiodol, it is termed TACE. The addition of chemotherapy aims to enhance the anti-tumoral action of ischemia. Usually, in TACE, anti-neoplasic drugs are mixed with lipiodol. By injecting the patient with a combination of anti-tumoral agents with the radio-opaque contrast agent lipiodol into the hepatic artery, drug delivery to tumor cells is expected to increase. Likewise, the chances of systemic side-effects related to chemotherapy are expected to decrease. Unfortunately, the use of either TAE alone or TACE, remains a controversial treatment approach for patients with HCC, because some randomized controlled trials have failed to disclose a significant benefit in terms of survival of treated patients as compared with untreated patients[34 , 35]. Moreover, several studies demonstrated disappointing results, showing that TACE enhances intrahepatic and

extrahepatic metastases, and even reduce survival[36]. Accordingly, anti-angiogenic therapy enhances the efficacy of transcatheter arterial embolization for HCC hepatocellular carcinomas[37]. Furthermore, severe side-effects produced by the arterial obstruction and by the toxicity of the injected anti-tumoral agents during the TACE procedure, counteract the anti-tumoral action resulting from arterial obstruction. It should be highlighted that the absence of effects due to chemotherapy is not the result of ineffective drug delivery but of the presence of MDR due to the over-expression of efflux pumps that belongs to the ABC superfamily of protein transporters, as well as to an abnormal p53 function that leads to an inhibition of apoptosis making tumor cells resistant to anti-tumoral treatment[38 - 40]. Dysfunctional p53 makes tumoral cells also less sensitive to hypoxia. Radiation therapy External beam radiation therapy: However, EBRT was mainly used in the palliative setting for metastatic disease because of an intolerance of the adjacent normal liver to tolerate radiation that precluded a more intense use of radiation[41]. In , the radiation therapy oncology group outlined the outcomes of a randomized clinical trial including radiotherapy of the whole-liver with a dose of 21 Gy in seven fractions or combined with the radiosensitizer misonidazole[42]. Although a whole-liver EBRT provided a significant palliative effect, the addition of misonidazole did not significantly improve the outcomes[43]. The dose-limiting complication of delivering EBRT to the liver is radiation-induced liver disease RILD a clinical entity characterized by the presence of anicteric hepatomegaly and ascites associated with high levels in sera of hepatic enzymes that may lead to liver failure and death[44]. Due to this reason, several approaches were designed by researchers at the University of Michigan to administer higher radiation doses to smaller liver portions, in order to produce greater tumor control rates without an increase in the damage to the liver parenchyma that is likely to be caused by radiation[45]. Based on the above, with the advent of intensity-modulated radiation therapy, image-guided radiation therapy and stereotactic body radiation therapy SBRT; as described below, separately , higher doses could be delivered safely since the radiation dose can be distributed tightly into the tumor while preserving normal tissue in the liver from the effects of high doses of radiation[41]. Intrahepatic radiotherapy, better known as radioembolization or selective internal radiation therapy SIRT , is a therapy based on the intrahepatic delivery of Yttrium Y -labeled microspheres into the arteries that supply blood to the tumor, where the microspheres come into contact with tumor cells which are hit by radiation emitted by the radioisotope[46]. The microspheres are an implantable medical device consisting of resin-based or glass-based biocompatible microspheres loaded with Y[47 , 48]. The process of release of the microspheres occurs by using a flexible catheter inserted into the femoral artery which is moved forward by the radiologist until the hepatic artery is reached[47 , 49]. The median overall survival ranged SIRT is a minimally invasive technique and a well-tolerated therapy. It is a new therapy for treating liver cancer and liver metastases originated from colorectal cancer. Clinical studies showed an increase in terms of survival when this technique is used in combination with chemotherapy. Noteworthy, SIRT tends to reduce the size of the tumor and allows some patients to become eligible for surgical resection[52]. As a means to ablate primary or metastatic liver tumors, technical advances in tumor localization and motion management were achieved. SBRT has become an optimistic approach for the treatment of liver cancer as a result of the complex character of liver tumor motion along with the priority of decreasing the volume irradiated to the minimum to reduce the probability of RILD. Focal, high dose SBRT delivers ablative doses in fewer fractions and highly conformational radiotherapy volumes[43]. To avoid damaging nearby critical structures and organs, doses are minimized using tight margins. A robust immobilization device is thus crucial to achieve a reproducible and accurate setup. A retrospective analysis carried out by Choi et al[53], demonstrated that a dose of 50 Gy of SBRT in 5 or 10 fractions for primary liver tumor produced a median survival of 20 mo. Another study carried out by Tse et al[54] using SBRT at a dose of Gy in 6 fractions, demonstrated that the median survival rate turned out to be Although liver metastasis is not the subject of the present review, it is noteworthy to point out that survival outcomes are better in patients with liver metastasis than with HCC. In both groups, there appears to be a dose-response for local control. For patients with Child-Pugh A cirrhosis, 48 Gy or higher distributed in 3 fractions is recommended. For patients with

Child-Pugh B cirrhosis, more fractionated schemes are suggested 5 fractions of 40 Gy, for example. For liver metastases, doses greater than 48 Gy divided into 3 fractions or Gy in one fraction is recommended[43]. Finally, with the use of innovative tools combined with radiotherapy such as advanced imaging and immunotherapy, further advances in liver cancer could be achieved.

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6: Indexes - [PDF Document]

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This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. This article has been cited by other articles in PMC. Abstract Fair allocation of organs to candidates listed for transplantation is fundamental to organ-donation policies. Processes leading to listing decisions are neither regulated nor understood. We explored whether patient characteristics affected timeliness of listing using population-based data on , adults hospitalized with liver-related disease in Pennsylvania. We linked hospitalizations to other secondary data and found 3, listed for transplants, 1, received transplants, and 57, died. Using competing-risks models, we found few overall differences by sex, but both black patients and those insured by Medicare and Medicaid combined waited longer before being listed. Patients with combined Medicare and Medicaid insurance, as well as those with Medicaid alone, were also more likely to die without ever being listed. The early time period from diagnosis to listing for liver transplantation reveals unwanted variation related to demographics that jeopardizes overall fairness of organ allocation and needs to be further explored. Introduction Because the demand for transplant services has always exceeded the supply of donor organs, the transplant community as well as policymakers have long recognized the need to ensure that the organ allocation system is efficient and equitable [1 â€” 6]. Yet, as noted by the Institute of Medicine, the transplant process involves numerous steps and inequities can take place anywhere along the way [8]. Historically, in cases where empirical data have shown systematic differences in waiting times or in the chances of receiving a transplant, UNOS has changed its policies to improve organ allocation procedures. Examples of changes include the institution of less stringent HLA-matching requirements for renal transplantation [9], the adoption of the final rule [6], and the use of the model of end-stage liver disease MELD scoring system for liver transplantation [10 , 11]. For renal transplantation, researchers have access to population-based data about the early steps of the transplant process from the US Renal Data System [12 â€” 14]. But for other types of solid organ transplantation, including liver transplantation, information about the early steps is generally unavailable, so oversight is restricted to steps after listing. We linked several secondary data sources to identify a statewide, population-based cohort of patients with liver-related conditions and followed the cohort through the following stages of the transplant process: We previously reported that demographics were important in determining the likelihood that patients with liver disease would be able to access the transplantation process for evaluation and listing, but not in affecting the likelihood that they would undergo transplantation once they were listed [15]. This initial analysis evaluated only whether or not patients progressed to specific stages of the transplantation process; because of missing data, it did not address matters related to timing and timeliness. In the current paper, we estimated the relationship between sociodemographics and the time required for patients to reach specific stages of the process. Specifically, we examined waiting times experienced by subsets of patients during 2 time periods. Data Sources and Data Management Our conceptual framework, data sources, and patient cohort have been described previously [15]. Briefly, we considered the stages in which a patient developed liver disease, was diagnosed, was referred to a transplant center and evaluated, was listed, and received a transplant. The PHC4 listed participating hospitals statewide during the study period. It provided us with data for all patients with liver-related stays between and To help identify and classify patients with liver disease, we developed a detailed list of diagnostic and procedural codes related to liver problems. Based on our previous work [17], we classified patients in terms of 9 major categories of disease: We excluded patients who were discharged in as well as those who had previously received a liver-transplant or been listed for one. This left us with a cohort of , patients with liver

disease from hospitals that had been newly diagnosed between and We linked the index hospitalization records of these patients to the following: For many patients in these data sets, the specific time at which some stages were reached was missing. However, the data were complete for the time of disease diagnosis, waitlisting, and transplantation. This allowed us to determine whether patients progressed to a subsequent stage and to measure the time intervals, in days, from diagnosis to listing early waiting time and from listing to receipt of a transplant later waiting time. In each case, there were 3 possible outcomes: The unit of analysis was the patient not the registration. Although the data were deidentified by the honest broker, multiple listings could be identified and reconciled using a pseudoidentifier for patients. In pooling the data sources, we applied 2 strategies for creating the longitudinal records for our patient cohort. First, we did not adjust the waiting times to account for periods when the patient was inactive a special status category for patients on the waiting list , which increases the estimates of later waiting times from listing to transplantation. Second, for patients with multiple listings, we took the earliest listing date available. Both of these conventions minimize early waiting time from diagnosis until listing and maximize later waiting times from listing to transplant, serving to bias against our hypothesis that early waiting times vary with socioeconomic variables but later waiting times do not. Our study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases and approved by the institutional review boards at the University of Pittsburgh and other participating transplant centers. We protected patient confidentiality by having the PHC4 serve as an honest broker to link records across data sources and provide our team with deidentified versions of the files. Statistical Analyses To characterize patients in terms of sociodemographic and clinical data, stage of the allocation process diagnosis, listing, and receipt of a transplant , waiting times, and outcomes, we used descriptive statistics. To compare the characteristics of subsets of patients at each stage of the process, we used univariable and multivariable survival models that included the following covariates: We included year of index hospitalization and also tested for interaction variables e. In the unadjusted case, we looked at differences in early waiting times based on the proportion of diagnosed patients who were placed on the transplantation waiting list within a specified period i. Similarly, we looked at differences in later waiting times by examining the proportion of listed patients who received transplants at these same intervals. In both cases, we controlled for the competing risk of death. In the adjusted models, we tested for differences in early waiting times by estimating the time to listing for the entire cohort, and we tested for differences in later waiting times by estimating time to transplant for patients on the waiting list. Results Table 1 shows data for 3 groupsâ€”the full cohort, the subset of patients listed for transplantation, and the final subset of patients who received transplantsâ€”stratified by sociodemographic and clinical characteristics. In all 3 groups, the largest proportions of patients were male, were 40â€”64 years of age, had commercial health insurance only, had a diagnosis of viral hepatitis, alcoholic liver disease, or autoimmune disorder, and had a moderate or severe level of illness. Because of the large sample size, between-group differences were statistically significant for all covariates. In general, however, differences between the first and second groups full cohort and listed patients were larger than differences between the second and third groups listed patients and transplant recipients. Full cohort of patients Patients who were listed for a transplant Patients who received a transplant Characteristic, no.

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The Clinician's Guide to Liver Disease by Thomas Faust available in Trade Paperback on www.enganchecubano.com, also read synopsis and reviews. The Clinicians Guide to Liver Disease is a user-friendly quick reference for the management of acute.

PQ , filed Jul. The aforementioned applications are expressly incorporated herein by reference in their entirety and for all purposes. TECHNICAL FIELD The present invention relates to pharmaceutical compositions suitable for the treatment of diseases in mammals, in particular to the treatment of chronic disorders associated with the presence of abnormal or an abnormal distribution of microflora in the gastrointestinal tract. The invention also relates to methods of treating such diseases. Pathophysiology of these disorders eludes logical explanation in spite of decades of research and millions of dollars of research funds. A common underlying factor shared by all these disorders observed by the present inventor is their onset or aggravation following some extraneous invading infection eg travellers diarrhoea. In all the disorders, a specific causal infection generally cannot be demonstrated due to our inability to detect infecting agents whose cultural characteristics are unknown to medical science. It is impractical to use long-term antibiotic therapy with its associated complications in such patients since cure is not obtained with its use. Some previous attempts have been made to alter the enteric microflora in order to eradicate such chronic infections. These measures nevertheless indicate that alteration of bacterial flora may effect dramatic clinical improvement in conditions characterised by chronic, resistant enterocolitic infection. However there remain many chronic disorders of uncertain aetiology or causation, which are resistant to cure by current therapeutic techniques. The use of probiotics in the human population has been largely confined to the inclusion in various foods of live organism of Lactobacilli and Bifidobacteria and less frequently Streptococcus faecalis or several strains of Escherichia coli. These organisms are thought to promote health via immune stimulation and reconstitution of what is presumed to be normal flora. Such usage stems back to the beliefs generated by Mechnikov in the early s. The use of probiotics to treat established infections in the gastrointestinal tract has been lesser but a growing part of the use of probiotics. Fungal agents such as Saccharomyces boulardii have been used to treat, albeit inefficiently, Clostridium difficile infection and Lactobacillus GG has also been used for this purpose Floch M. Probiotics and Dietary Fibre. J Clin Gastroenterol ; 27 2: Various patents have claimed the use of probiotics for narrow disease conditions including treatment of Clostridium difficile with a combination of Vancomycin and butyric acid bacteria U. Enterococcus faecium has been claimed to be useful in alleviating symptoms of Irritable Bowel Syndrome in humans U. Clostridium butyricum as a single agent has been claimed to be a biological intestinal antiseptic for treatment of bacterial food poisonings U. This patent also advocated the use of dried, reconstituted faeces or a synthetic mixture comprising Bacteroides sp. Such a replacement mixture has the dual ability of displacing pathogenic bacteria, frequently Clostridial in nature and also establishing a normal environment in which commensal bacteria can establish. Such a treatment permits long-term recovery both from gastrointestinal disorders and from systemic afflictions not hitherto considered to be caused by harmful enteric flora. Autism is a regressive disorder of childhood, affecting boys four times more often than girls. It has been observed that the onset of autism is often preceded by broad spectrum antibiotic use eg for recurrent ear infections. Antibiotic therapy is non-discriminatory in its action and apart from treating the ear infection the microflora of the healthy gastrointestinal tract can be severely disrupted by such treatment. This creates an environment where vulnerability to opportunistic microorganism colonisation is heightened. Clostridium tetani is a widely distributed, spore forming anaerobe. Toxigenic strains of Clostridium tetani produce the extremely potent tetanus neurotoxin which is known to enter the central nervous system from the intestinal tract via the vagus nerve Hensel B et al. Naunyn Schmeidebergs Arch Pharmocol ; Bolte Med Hypotheses ; Others have also raised the possibility of clostridia in general as a cause of disease Borriello SP. Clin Infect Dis ; Suppl 2: All children in the trial had had antecedent broad-spectrum

antibiotic exposure, followed by chronic persistent diarrhoea and then onset of autistic features. Although significant post-treatment improvement was noted, all children eventually regressed towards baseline. It is on the background of these known facts and later the results of trials of treatment, that the present invention was formulated. However, not only did their IBS improve dramatically but also their autistic features progressively regressed. Continuing improvement was observed to occur over 12 months of treatment. The inclusion within this specification of reference to published documents is not to be taken to be an admission that any one or more of those documents, nor the disclosure of any one or more of those documents, is part of the common general knowledge. It is a further object of the invention to propose the use of these pharmaceutical compositions in various disease states which have not previously been considered to owe their causation to the presence of abnormal flora in the gastrointestinal tract. The invention has also been found to relate to other gastrointestinal disorders of unexplained aetiology such as polyposis coli and colonic polyps, which may well be influenced by the local bowel microflora. The links between the intestine and joint disease are also recognised. Other chronic conditions such as acne, and chronic idiopathic pseudo-obstructive syndrome, may well be influenced by similar mechanisms. The present inventor therefore recognised the need to find a curative therapy for these wide ranging disease processes associated with considerable morbidity. Thus, by incorporation of Clostridia spp. Without the addition specifically of Clostridia species, the use of probiotic mixtures, eg such as those of bacteroides and Escherichia coli failed to have the necessary impact on the above-mentioned clinical disorders for the treatment to be clinically useful. It required a prior purging of the gut of its presumably infected and abnormal bowel flora, re colonisation with bacteroides and Escherichia coliâ€”the main components of lower intestinal tract, and ongoing feeding of patients with such bacteria until colonisation was established. The use of Clostridia appears to be the mainstay of this new therapy and the Clostridia appear to have power of themselves to remove offending bacterial species which may be responsible for the underlying condition presumably pathogenic clostridiaâ€”yet to be identified scientifically. In fact, such a therapy becoming available has permitted or allowed greater understanding of the pathogenesis of many other conditions which hitherto were thought to be caused by degenerative, inflammatory, or auto immune mechanisms. In a preferred form the composition further comprises one or more additional viable non-pathogenic or attenuated pathogenic microorganisms selected from the group consisting of Bacteroides, Eubacteria, Fusobacteria, Propionibacteria, Lactobacilli, anaerobic cocci, Ruminococcus, Escherichia coli, Gemmiger, Desulfomonas, Peptostreptococcus, species and, more specifically, bacteria selected from Table 1. Preferably fungi are also present such as Monilia. In a preferred form the composition comprises Clostridia, Bacteroides, Peptostreptococcus, Escherichia coli, Bifidobacterium, and Lactobacillus. In a more preferred form the composition comprises Clostridium innocuum, Clostridium bifermentans, Clostridium butyricum, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, one or more strains of Escherichia coli, and one or more strains of Lactobacillus. Alternatively, in a preferred form the composition comprises Clostridium bifermentans, Clostridium innocuum, and Clostridium butyricum in combination one or more strains of Escherichia coli, one or more strains of bacteroides and Peptostreptococcus productus. In a preferred form the other viable non-pathogenic or attenuated pathogenic microorganism is selected from the group consisting of Clostridia, Peptostreptococcus, Bifidobacterium, and Lactobacillus. The fresh homologous faeces does not include an antibiotic resistant population. Typically, the composition of the first or second embodiments of the invention is a synthetic faecal composition. In a preferred form the synthetic faecal composition comprises a preparation of viable flora which preferably in proportional content, resembles normal healthy human faecal flora which does not include antibiotic resistant populations. Suitable microorganisms may be selected from the following: Bacteroides, Eubacteria, Fusobacteria, Propionibacteria, Lactobacilli, anaerobic cocci, Ruminococcus, Escherichia coli, Gemmiger, Clostridium, Desulfomonas, Peptostreptococcus, Bifidobacterium, species and, more specifically, bacteria selected from Table 1. In a preferred form the composition of the first or second embodiments of the invention comprises a liquid culture. Preferably, the composition of the first or the second embodiments of the present invention is lyophilised,

pulverised and powdered. It may then be infused, dissolved such as in saline, as an enema. Alternatively the powder may be encapsulated as enteric-coated capsules for oral administration. These capsules may take the form of enteric-coated microcapsules. As a powder it can preferably be provided in a palatable form for reconstitution for drinking or for reconstitution as a food additive. The composition can be provided as a powder for sale in combination with a food or drink. Typically, the food or drink is a dairy-based product or a soy-based product. The invention therefore also includes a food or food supplement containing a composition according to the first or second embodiment. In a preferred form the food or food supplement contains enteric-coated microcapsules of the composition of the invention. In a preferred form the food is yogurt. The powder may be reconstituted also to be infused via naso-duodenal infusion. The composition can be combined with other adjuvants such as antacids to dampen bacterial inactivation in the stomach. Acid secretion in the stomach could also be pharmacologically suppressed using H2-antagonists or proton pump inhibitors. Typically, the H2-antagonist is ranitidine. Typically the proton pump inhibitor is omeprazole. The composition of the first or second embodiments of the invention is therefore preferably in the form of: In its preferred form the treatment should effect a cure of the symptoms of such disorders. The method of the present invention is applicable to animals in general, in particular humans and economically significant domestic animals. In the case of humans, the present invention encompasses methods of treatment of chronic disorders associated with the presence of abnormal enteric microflora. Such disorders include but are not limited to those conditions in the following categories: The above disorders are all characterised by their response to treatment with the method of the present invention. Typically the change in enteric flora comprises introduction of an array of predetermined flora into the gastro-intestinal system, and thus in a preferred form the method of treatment comprises substantially completely displacing pathogenic enteric flora in patients requiring such treatment. Furthermore, in some of these disorders a short course of antibiotics prior to probiotic treatment may be preferred to rid tissue-invasive pathogens originating in the bowel lumen. Typically the antibiotic is an anti-Clostridial antibiotic such as vancomycin, rifampicin, and nitroimidazole or chloramphenicol. Typically the nitroimidazole is metronidazole. In a preferred form of the invention, the method of treatment or prophylaxis further includes administration of at least one acid suppressant prior to administering, or in co-administration with, the composition of the invention. The introduction of the composition into the gastro-intestinal system can be effected by enema or per-colonoscope, via intubation of the small bowel using for example a large bore catheter equipped with distal balloon to effect rapid passage down the jejunum, or via the oral route with enteric-coated capsules, including enteric-coated microcapsules, or via the oral route with a supplemented food or drink. In a preferred form the supplemented food or drink is a dairy-based or soy-based product. Typically the supplemented food product is yogurt. According to the method of the invention each dose of the composition is in the range of about cells to about cells. Preferably each dose is in the range of about cells to about cells. More preferably each dose is in the range of about cells to about cells. In a preferred form of the invention an initial treatment regimen consisting of about cells per dose is administered about 3 to 6 times per day for a period sufficient to stabilise the gut flora. According to the method of the invention the treatment regimen may then comprise a maintenance dose of about cells per day. Furthermore the present invention also relates to the treatment of animals, in particular to the treatment of gastrointestinal disorders in economically important domestic animals, such as cattle, sheep, horses, pigs, goats etc. The method of the present invention has been found to be especially useful in the treatment of the various forms of necrotising enterocolitis which can be a major problem in animal stocks. Obviously in the treatment of animals the appropriate composition of microflora will vary according to the species being treated and the constituent normal flora known to inhabit the gut.

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Abstract Bile is a unique and vital aqueous secretion of the liver that is formed by the hepatocyte and modified down stream by absorptive and secretory properties of the bile duct epithelium. The bile-secretory unit consists of a canalicular network which is formed by the apical membrane of adjacent hepatocytes and sealed by tight junctions. Canalicular bile secretion is determined by both bile salt-dependent and independent transport systems which are localized at the apical membrane of the hepatocyte and largely consist of a series of adenosine triphosphate-binding cassette transport proteins that function as export pumps for bile salts and other organic solutes. These transporters create osmotic gradients within the bile canalicular lumen that provide the driving force for movement of fluid into the lumen via aquaporins. Species vary with respect to the relative amounts of bile salt-dependent and independent canalicular flow and cholangiocyte secretion which is highly regulated by hormones, second messengers, and signal transduction pathways. Most determinants of bile secretion are now characterized at the molecular level in animal models and in man. Genetic mutations serve to illuminate many of their functions. Introduction Bile formation is a unique function of the liver which is vital to survival of the organism. Knowledge of the mechanism of bile formation has progressed rapidly in recent years and has provided the basis for further diagnosis and treatment of cholestatic disorders. Here, we review historical milestones in these developments and summarize current knowledge in this field. Bile is a complex aqueous secretion that originates from hepatocytes and is modified distally by absorptive and secretory transport systems in the bile duct epithelium. Bile then enters the gallbladder where it is concentrated or is delivered directly to the intestinal lumen. Bile serves a number of important functions. The importance of bile secretion to the health of the organism becomes most evident when this secretion is impaired by developmental, genetic or acquired cholestatic diseases. This is most dramatically demonstrated by children born with biliary atresia who develop progressive cholestatic liver injury, biliary cirrhosis, and ultimately liver failure and death. Historical Aspects Although the importance of bile has been recognized since antiquity 60 little was known about the fundamental mechanisms that produced this vital secretion until the middle of the 20th century. Knowledge lagged far behind the understanding of other body fluids such as urine. Thus for many years the scientific literature was largely limited to reports of the chemical composition of bile Since there was no ability to sample or assess the primary source of bile, these analyses were the combined result of hepatocyte bile that was modified further by secretory and absorptive properties of the bile duct epithelium A mechanistic understanding of biliary secretion in the modern era began with earnest with the work of Ralph Brauer and Ivar Sperber. Brauer was a physiologist who worked for the US Navy. Using the isolated perfused rat liver, he demonstrated that bile was secreted against pressures that exceeded the vascular perfusion pressure Thus bile was not formed by hydrostatic filtration as was urine. This landmark study clearly demonstrated that the formation of bile was an energy dependent process, findings that were later confirmed using metabolic poisons that resulted in inhibition of bile production 65 , His report was heavily influenced by prior work of many different investigators, particularly early renal physiologists but included his own studies of the secretion of phenol red in urine and bile in the anesthetized chicken. A few years earlier, in , Pappenheimer had proposed that water could flow across a semipermeable membrane as a result of the creation of osmotic gradients It is reasonable to assume that Sperber was influenced by this publication and concluded that the concentrative transport of solutes in bile created osmotic gradients that then stimulated the passive diffusion of water and electrolytes across the semipermeable canalicular membrane into bile The primary event of bile formation would be the active transfer from cells or through cells of bile acids and possibly other, though quantitatively less important compounds into the bile capillaries. Henry Wheeler and his colleagues were the first to measure the biliary clearance of radiolabled inert solutes such as erythritol or

mannitol. These small molecules were believed to enter bile at the level of the bile canaliculus, either across the tight junction barrier or through rapid transcellular pathways in the hepatocytes. Using these techniques of solute clearances, which were originally adopted from studies of renal clearances, Wheeler and subsequent investigators were able to characterize canalicular bile production and distinguish it from fluid secretion formed more distally by the bile duct epithelium Initially, these solute clearances were performed in dogs and rats with biliary fistulae, but were subsequently used to quantify the components of bile in patients with in-dwelling t-tubes following routine cholecystectomy At this point, attention was focused on the mechanism of the bile salt-independent component of canalicular bile. There was considerable interest in the role of sodium transport and many biliary physiologists believed that BSIF might be generated by active extrusion of sodium ions into the canalicular lumen. This milestone discovery indicated that the liver was physiologically similar to other polarized epithelia with respect to the location of specific transport proteins, despite the unique localization of the apical canalicular membrane encircling the hepatocyte like a belt This finding led to the realization that the inwardly directed sodium gradient, generated by the sodium pump, could be utilized as a secondary driving force when coupled to other solutes and provided a mechanistic explanation for the previously demonstrated dependence of hepatic uptake of conjugated bile salts on the presence of sodium ions 29 , The ability to separate hepatocyte secretory events from those at the level of the cholangiocyte was greatly enhanced by the recognition in that some hepatocytes, when isolated from the liver by collagenase perfusion, remained attached and formed couplets or triplets which retained apical polarity between the adjacent cells These canalicular lumens expanded with time in culture and provided a novel in vitro model that enabled studies of bile secretion to be made without the confounding effects of blood flow and pressure or the contribution of the bile ducts , , Electrophysiological studies, including measurements of the transcanalicular membrane electric potential, confirmed that the sodium pump was electrogenic and that together with potassium channels in the basolateral membrane, generated both chemical and electrical driving forces that could be used for transmembrane transport of organic solutes. This technical advance then enabled transport functions to be characterized in canalicular membrane vesicles 82 , an approach that ultimately led to another major milestone, the recognition that bile salts and other solutes were transported into bile largely by adenosine triphosphate ATP -dependent transport mechanisms 3 , , , rather than driven by the cellular electrical potential as originally believed , Cell isolation techniques also led to the isolation of purified populations of cholangiocytes 12 , , , and resulted in the finding that they could form spheroids with enclosed lumens when placed in culture These isolated bile duct units IBDUs enabled physiologic studies to be performed that characterized the role of hormones such as secretin, bombesin, vasoactive peptide VIP , and others, as well as the function of ion transporters, in the generation of bicarbonate secretion from this epithelia 16 , 74 , , Since the s molecular cloning techniques and cellular expression systems revolutionized our understanding of the mechanisms of bile formation and the molecular causes of cholestasis Today most of the major membrane transport proteins that determine both the hepatic uptake of organic solutes as well as bile salt-dependent and bile salt-independent canalicular and cholangiocyte excretion are now characterized at the molecular level. What follows is a summary of the current state of knowledge in this field based largely on these historical milestones. The remaining major portions of the cell membrane consist of the basal membrane that faces the blood sinusoids and contains many microvilli, and the smooth lateral membrane that lines the intercellular space Fig. This is the only physical barrier between the blood and the canalicular lumen Fig. The structure of the tight junction is best visualized in freeze fracture replicas, which reveal a series of four to five cross-linked parallel strands Fig. These strands are primarily composed of globular proteins known as occludins and claudins , Fig. Tight junctions hold the hepatocytes together, as well as provide a barrier that prevents bile acids and other large solutes from diffusing from bile, while at the same time allowing the passage of small ions. Claudins and occludins are connected to cytoskeletal proteins ZO-1 and ZO-2 on the cytoplasmic side of the membrane as part of the tight junction complex. This intercellular barrier is negatively charged which facilitates the passage of small ions, particularly sodium, but is impermeant to molecules the

size of proteins. During cholestatic liver injury, the tight junction may be disrupted, resulting in regurgitation of bile contents into the intercellular space and dissipation of the intracanalicular osmotic gradients upon which the secretion of bile depends

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9: Table of contents for The clinician's guide to liver disease

Reduced BMD has been shown in some cross-sectional studies with patients suffering from viral cirrhosis, primary biliary cirrhosis, or primary sclerosing cholangitis [11, 13, 19].

The compositions further comprise one or more additional viable non-pathogenic or attenuated pathogenic microorganisms selected from the group consisting of Bacteroides, Eubacteria, Fusobacteria, Propionibacteria, Lactobacilli, anaerobic cocci, Ruminococcus, E. The present invention also provides pharmaceutical compositions suitable for the treatment of the same chronic diseases comprising viable non-pathogenic or attenuated pathogenic Escherichia coli, at least one strain of viable non-pathogenic or attenuated pathogenic Bacteroides and at least one strain of viable non-pathogenic or attenuated pathogenic microorganism. PQ , filed Jul. The aforementioned applications are expressly incorporated herein by reference in their entirety and for all purposes. TECHNICAL FIELD The present invention relates to pharmaceutical compositions suitable for the treatment of diseases in mammals, in particular to the treatment of chronic disorders associated with the presence of abnormal or an abnormal distribution of microflora in the gastrointestinal tract. The invention also relates to methods of treating such diseases. Pathophysiology of these disorders eludes logical explanation in spite of decades of research and millions of dollars of research funds. A common underlying factor shared by all these disorders observed by the present inventor is their onset or aggravation following some extraneous invading infection eg travelers diarrhoea. In all the disorders, a specific causal infection generally cannot be demonstrated due to our inability to detect infecting agents whose cultural characteristics are unknown to medical science. It is impractical to use long-term antibiotic therapy with its associated complications in such patients since cure is not obtained with its use. Some previous attempts have been made to alter the enteric microflora in order to eradicate such chronic infections. These measures nevertheless indicate that alteration of bacterial flora may effect dramatic clinical improvement in conditions characterised by chronic, resistant enterocolitic infection. However there remain many chronic disorders of uncertain aetiology or causation, which are resistant to cure by current therapeutic techniques. The use of probiotics in the human population has been largely confined to the inclusion in various foods of live organism of Lactobacilli and Bifidobacteria and less frequently Streptococcus faecalis or several strains of Escherichia coli. These organisms are thought to promote health via immune stimulation and reconstitution of what is presumed to be normal flora. Such usage stems back to the beliefs generated by Mechnikov in the early s. The use of probiotics to treat established infections in the gastrointestinal tract has been lesser but a growing part of the use of probiotics. Fungal agents such as Saccharomyces boulardii have been used to treat, albeit inefficiently, Clostridium difficile infection and Lactobacillus GG has also been used for this purpose Floch M. Probiotics and Dietary Fibre. J Clin Gastroenterol ; 27 2: Various patents have claimed the use of probiotics for narrow disease conditions including treatment of Clostridium difficile with a combination of Vancomycin and butyric acid bacteria U. Enterococcus faecium has been claimed to be useful in alleviating symptoms of Irritable Bowel Syndrome in humans U. Clostridium butyricum as a single agent has been claimed to be a biological intestinal antiseptic for treatment of bacterial food poisonings U. This patent also advocated the use of dried, reconstituted faeces or a synthetic mixture comprising Bacteroides sp. Such a replacement mixture has the dual ability of displacing pathogenic bacteria, frequently Clostridial in nature and also establishing a normal environment in which commensal bacteria can establish. Such a treatment permits long-term recovery both from gastrointestinal disorders and from systemic afflictions not hitherto considered to be caused by harmful enteric flora. Autism is a regressive disorder of childhood, affecting boys four times more often than girls. It has been observed that the onset of autism is often preceded by broad spectrum antibiotic use eg for recurrent ear infections. Antibiotic therapy is non-discriminatory in its action and apart from treating the ear infection the microflora of the healthy gastrointestinal tract can be severely disrupted by such treatment. This creates an environment where vulnerability to opportunistic microorganism colonisation is heightened. Clostridium

tetani is a widely distributed, spore forming anaerobe. Toxigenic strains of Clostridium tetani produce the extremely potent tetanus neurotoxin which is known to enter the central nervous system from the intestinal tract via the vagus nerve Hensel B et al. Naunyn Schmeidebergs Arch Pharmocol ; Bolte Med Hypotheses ; Others have also raised the possibility of clostridia in general as a cause of disease Borriello S P. Clin Infect Dis ; Suppl 2: All children in the trial had had antecedent broad-spectrum antibiotic exposure, followed by chronic persistent diarrhoea and then onset of autistic features. Although significant post-treatment improvement was noted, all children eventually regressed towards baseline. It is on the background of these known facts and later the results of trials of treatment, that the present invention was formulated. However, not only did their IBS improve dramatically but also their autistic features progressively regressed. Continuing improvement was observed to occur over 12 months of treatment. The inclusion within this specification of reference to published documents is not to be taken to be an admission that any one or more of those documents, nor the disclosure of any one or more of those documents, is part of the common general knowledge.

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