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GUIDELINES AND CONSENSUS STATEMENTS

Approach to the patient with cholestasis and jaundice syndrome. Joint AMH, AMG, and AMEG scientific position statement☆

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KEYWORDS
Cholestasis;
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Abstract: The term cholestasis refers to bile acid retention, whether within the hepatocyte or in the bile ducts of any caliber. Biochemically, it is defined by a level of alkaline phosphatase that is 1.67-times higher than the upper limit of normal. Cholestatic diseases can be associated with an inflammatory process of the liver that destroys hepatocytes (hepatitis), withjaundice (yellowing of the skin and mucus membranes, associated with elevated serum bilirubin levels), or with both, albeit the three concepts should not be considered synonymous. Cholestatic diseases can be classified as intrahepatic or extrahepatic, depending on their etiology. Knowing the cause of the condition is important for choosing the adequate diagnostic studies and appropriate treatment in each case. A complete medical history, together with a thorough physical examination and basic initial studies, such as liver ultrasound and liver function tests, aid the clinician in deciding which path to follow, when managing the patient with cholestasis. In a joint effort, the *Asociación Mexicana de Hepatologá* (AMH), the *Asociación Mexicana de Gastroenterologá* (AMG) and the *Asociación Mexicana de Endoscopia Gastrointestinal* (AMEG) developed the first Mexican scientific position statement on said theme.

PALABRAS CLAVE
Colestasis;
Ictericia;
Hígado;
Bilis;
ácido ursodeoxicólico

Abordaje del paciente con colestasis y síndrome ictérico. Posicionamiento científico conjunto AMH, AMG, AMEG

Resumen El término colestasis se refiere a la retención de ácidos biliares ya sea dentro del hepatocito o en los ductos biliares de cualquier calibre. Por laboratorio, se define por la elevación de fosfatasa alcalina arriba de 1.67 veces su valor normal. Las enfermedades colestásicas pueden asociarse a un proceso inflamatorio de la glándula hepática que provoca destrucción de los hepatocitos (hepatitis), a ictericia (coloración amarillenta de piel y mucosas asociada a elevación en niveles séricos de bilirrubinas) o ambas, aunque estos tres conceptos no deben considerarse sinónimos. Los padecimientos colestásicos pueden clasificarse como intra o extrahepáticos dependiendo de su etiología, y esto es importante para elegir los estudios diagnósticos adecuados y la terapéutica indicada en cada uno de los casos. Una historia clínica completa, aunada a exploración física exhaustiva y estudios iniciales básicos como el ultrasonido hepático y las pruebas de funcionamiento del hígado pueden ayudar al clínico a decidir el camino a seguir al enfrentarse al paciente con colestasis. La Asociación Mexicana de Hepatología, la Asociación Mexicana de Gastroenterología y la Asociación Mexicana de Endoscopia Gastrointestinal decidieron trabajar en el primer posicionamiento científico mexicano sobre este tema.

Introduction

Cholestasis is a decrease in bile formation or flow at the level of the hepatocyte or cholangiocyte. It manifests clinically as fatigue, pruritus, and its most obvious symptom, jaundice. Biochemically, it is defined as a level of alkaline phosphatase (ALP) that is 1.67-times higher than the upper limit of normal (ULN). The causes of cholestatic disease are multiple, and so accurate diagnosis is essential for establishing the appropriate treatment.

Hence, the Asociación Mexicana de Hepatología (AMH), the Asociación Mexicana de Gastroenterología (AMG), and the Asociación Mexicana de Endoscopá Gastrointestinal (AMEG) summoned a multidisciplinary group of 24 specialists to review and discuss the scientific evidence on the approach to and diagnosis of the patient with cholestasis and jaundice syndrome.

Methods

A scientific position statement was drafted, based on an extensive review of the literature and expert recommendations. Three coordinators (Velarde Ruiz Velasco, Rizo Robles Teresa, Trujillo Benavides Omar Edel) were named, who carried out a review of the bibliography, utilizing the following terms and their Spanish equivalents as the search criteria: ''cholestasis'', ''hepatitis'', ''jaundice'', ''jaundice syndrome'', ''hyperbilirubinemia'', ''alkaline phosphatase'', and ''bile obstruction''. The search was conducted using the PubMed y EMBASE databases and included articles pub-

lished from January 1990 to June 2019. All texts in English and Spanish were included. Preference was given to consensuses, guidelines, systematic reviews, and meta-analyses, but the search was not limited to those types of articles. Complementary electronic and manual searches for all articles published up to July 2018 that the coordinators considered relevant were also carried out. The complete bibliography was made available to the working group, throughout the entire process. The decision was made to produce a position statement, rather than guidelines, due to the fact that no prospective studies or experimental evidence were included in the information evaluated.

After the articles were reviewed, questions were formulated on the different topics. They were discussed and answered at a face-to-face meeting that took place in San Miguel de Allende, Guanajuato, Mexico, on July 26 and 27, 2019, resulting in the narrative review presented below.

How are cholestasis, hepatitis, and jaundice defined?

Cholestasis is a decrease in bile formation or flow at the level of the hepatocyte or cholangiocyte.[1] It can result from: 1) hepatocellular and/or cholangiocellular secretory defects or 2) from bile duct obstruction due to ductal lesions, stones, or tumors. It can also be related to mixed mechanisms in conditions, such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Its main clinical manifestations are fatigue, pruritis, and jaundice, and it is characterized by ALP levels 1.67-times higher than the ULN, as well as elevated levels of gamma-glutamyl transpeptidase (GGT). It can also be classified by origin (intrahepatic or extrahepatic) or duration (acute: less than 6 months; chronic: more than 6 months).[2]

Jaundice is a clinical manifestation of diseases of the liver and biliary tree that consists of a yellowing of the skin, mucus membranes, and organic fluids due to elevated bilirubin levels in blood, with a total bilirubin level higher than 2.5 mg/dl.

Hepatitis is an inflammatory process of the liver that is characterized by high aminotransferase (transaminase) levels. It can spontaneously remit or progress to fibrosis (scarring), cirrhosis, or hepatocellular cancer. Hepatitis viruses are the main cause, but it can also result from other infections, toxic substances (e.g., alcohol or certain drugs), or autoimmune diseases. Importantly, a high bilirubin level *per se* does not determine the diagnosis of hepatitis, and many hepatitis infections do not increase bilirubin levels.[2]

What is the approach to the patient with extrahepatic cholestasis?

Extrahepatic cholestasis is caused by obstruction of the extrahepatic bile ducts.[3] Choledocholithiasis, biliary stricture, tumors (cholangiocarcinoma, carcinoma of the head of the pancreas, ampulloma, etc.) are among the main causes. Other less common causes are parasitosis or autoimmune diseases. Radiologic images and forward-viewing endoscopy play a central role in the etiologic evaluation of extrahepatic cholestasis, and are also useful for determining treatment strategies.[4] Diagnostic imaging studies include transabdominal ultrasound, which is the initial radiologic study of choice, even though it is operator-dependent; computed tomography (CT) cholangiography, with > 95% sensitivity for choledocholithiasis and neoplasms, but important exposure to radiation; and magnetic resonance (MR) cholangiography, with > 94% sensitivity and > 96% specificity for biliary tree disease and lithiasis, no radiation exposure, but higher cost, less availability, and no therapeutic capacity.[5]

With respect to endoscopy, the procedure that has diagnostic and therapeutic capacities for resolving the majority of causes of bile duct obstruction is endoscopic retrograde cholangiopancreatography (ERCP). It combines endoscopy and radiology to extract stones, place self-expandable plastic or metallic stents, or enable the passage of a cholangioscope to evaluate and dilate strictures or perform intraductal lithotripsy.[6]

Endoscopic ultrasound (EUS) is a procedure that utilizes an endoscope, with an ultrasound transducer installed on its tip, that can define bile duct and pancreatic duct anatomy, view the parenchyma of the liver and pancreas, and detect choledocholithiasis, microlithiasis, and pancreatic lesions. EUS as the initial method is more cost-effective in patients with an estimated probability of common bile duct stones below 61%. It has been shown to be superior to CT, magnetic resonance imaging (MRI), or abdominal ultrasound for tumor staging and can determine the endoscopic resectability of tumors.[7]

Cholangioscopy is an endoscopic procedure that employs a thin endoscope that is introduced by the working channel of a duodenoscope, up to the interior of the bile ducts. Both instruments can be operated by a single operator. The intraductal mucosa and lesion characteristics can be viewed and it enables the evaluation of bile duct stricture of undetermined etiology. It also allows lithotripsy, whether electrohydraulic or laser, to be performed in cases of very large bile duct stones.[8,9]

What is the approach to the patient with intrahepatic cholestasis?

The first step in diagnosing intrahepatic cholestasis is the appropriate interpretation of the biochemical tests.[10,11]

Hepatocellular damage is predominantly characterized by high aminotransferase levels, in which elevations 10-times higher than the ULN suggest acute or severe lesion, e.g., due to drugs, acute viral hepatitis, or ischemia.[12–14] Cholestasis tends to predominantly elevate ALP (> 1.5 above the ULN). Nevertheless, ALP is nonspecific, and levels can be high in bone disease, intestinal disease, or during pregnancy (placenta). The alanine aminotransferase (ALT)/ALP ratio is generally < 2 in cholestasis.[15,16] The concomitant elevation of GGT (> 3-times higher than the ULN) and ALP supports the diagnosis of cholestasis but the isolated elevation of GGT is poorly specific for cholestasis and can be due to alcohol or medication use.[14] The isolated elevation of ALP can occur in infrequent diseases, such as progressive familial intrahepatic cholestasis (PFIC), type 1 and type 2.[17]

Bilirubin levels can be higher in hepatocellular lesions, as well as in cholestasis. The predominance of direct or conjugated bilirubin usually indicates hepatocellular or cholestatic lesion, whereas the predominance of indirect or

nonconjugated bilirubin can present in Gilbert syndrome (5% of the general population) or can be due to hemolysis or acute skeletal muscle lesion.[18]

Hypoalbuminemia tends to indicate advanced liver disease, but it is not specific either, and can be altered by chronic kidney disease, pregnancy, inflammation, malnutrition, and protein-losing intestinal diseases, among others.[14]

Among the possible causes of intrahepatic cholestasis are viral or toxic hepatitis, liver ischemia, sepsis, tumor dissemination, drug or herb-induced injury, and autoimmune diseases, such as PBC, PSC, autoimmune hepatitis (AIH) or disease due to IgG4.[19–26]

Drug-induced idiosyncratic injury is a rule-out diagnosis. Its clinical presentation is variable and there is not much available information on its risk factors or diagnostic tests.[27]

Hepatocellular lesion can be differentiated from cholestatic damage by calculating the R ratio, which utilizes ALP and ALT levels and is described as: (ALT value/ULN of ALT)/(ALP value/ULN of ALP). The hepatocellular lesion presents a predominant increase in serum aminotransferases and an R criterion > 5, whereas cholestasis presents an R value < 2. A mixed hepatic lesion pattern has an R criterion > 2 but < 5.[28,29] The most common method for evaluating causality between liver injury and a presumed medication is the Roussel Uclaf Causality Assessment Method (RUCAM).[30,31] Consulting LiverTox, a database of approximately 1,200 over-the-counter medications, herbal products, nutritional supplements, metals, and toxins, is recommended because it provides an overview of drug-induced liver damage.[32]

In *intrahepatic cholestasis of pregnancy*, there can be an increase in the total bilirubin level < 6 mg/dl, ALP, and elevated aminotransferases, which normalize 6 to 8 weeks after childbirth. Diagnosis is confirmed by bile acid levels 10 to 25-times higher than the ULN (> 10 μmol/l). It presents in the third trimester, rarely presents before gestation week 26, and is more common in multiparous women and during the winter months. There is an occasional history of cholestasis due to oral contraceptive use. Pruritus is the cardinal symptom and is predominant on the palms of the hands and soles of the feet.[31–33]

How should patients with intrahepatic cholestasis be treated?

Ursodeoxycholic acid (UDCA) has different well-demonstrated biochemical activities, such as decreasing bile acid hydrophobicity, stimulating bile flow, and inducing choleresis. It is hepatoprotective, thanks to its anti-apoptotic activity, which reduces the injury caused by free radicals, thus presenting anti-inflammatory and immunomodulating activity at the level of the liver.[34–41] UDCA was approved in 1997 for use in PBC at a dose of 13-15 mg/kg/day. Regarding PSC, some experts still utilize UDCA at doses of 17-23 mg/kg/d, hoping to reduce serum ALP levels, given that a survival benefit has been shown in patients with a spontaneous normalization of ALP or resulting from treatment with UDCA.[42–44]

Obeticholic acid (OCA) is a semi-synthetic hydrophobic bile acid analogue that is very selective for the farnesoid X receptor (FXR) and impacts inflammation, metabolic regulation, and liver fibrosis.[45] OCA combined with UDCA, or as monotherapy, aids in normalizing ALP and total bilirubin levels and reduces the risk for progression to PBC.[46,47] The initial dose of OCA is 5 mg once-daily. According to a tolerability evaluation at 6 months, the dose should be increased to 10 mg once-daily to obtain the optimum response at 12 months. Treatment is associated with the exacerbation of pruritus.

Other therapeutic options being studied are fibrates (mainly *bezafibrate*, alone or combined with UDCA), *budesonide* (a synthetic corticoid that undergoes first-pass metabolism in the liver and has fewer adverse effects than other steroids), and *colchicine* (for its apparent immunomodulating effect and potentially antifibrotic effect). Those therapies are still in the experimental stage, they have important adverse effects, and their use outside of clinical trials is not yet recommended. Colchicine, in particular, is not an approved therapy for PBC. However, a recent study on the usefulness of budesonide in patients with PBC that did not respond adequately to UDCA showed that, despite no significant histologic changes, treatment with budesonide was associated with biochemical improvement in the secondary analysis.[48–54]

As to the usefulness of hepatoprotective agents, the mechanism of action of *silymarin*[55,56] appears to be multifactorial. It stabilizes membranes, has properties for eliminating free radicals, and shows antifibrotic and anti-inflammatory properties. Nevertheless, there are few studies that explore the effectiveness and safety of silymarin in patients with intrahepatic cholestasis, and so there is no indication for its use in said disease.[57–61]

Metadoxine has antioxidant activity and is utilized in alcohol-induced liver disease. It has recently been tested in nonalcoholic fatty liver, but no studies have been published on its use in intrahepatic cholestasis in humans.[62]

Oral and parenteral *ademetionine* has been shown to be effective in the treatment of intrahepatic cholestasis of pregnancy,[63] but its usefulness has not been shown in cholestatic disease in other groups.

How should symptoms associated with cholestasis be treated?

Quality of life in subjects with some type of cholestatic compromise, especially chronic involvement, can be reduced due to certain inherent manifestations of the condition. The occurrence and severity of some of those manifestations is separate from the advance of the liver disease.[64]

Pruritus. The majority of patients with chronic cholestatic disease present, at least transitorily, with pruritus. The spectrum can range from mild forms to incapacitating variants that result in sleep deprivation and suicidal ideation. When incapacitating and refractory, pruritus is considered an indication for liver transplantation.

Cholestyramine consumption can produce discomfort and constipation. Care must be taken to take it 4 h before other medications, such as UDCA, thyroxine, digoxin, contraceptives, and fat-soluble vitamins. The recommended dose is 0.25-0.5 g/kg/day (maximum 16 g) divided into 3-4 doses (30 min before and after meals) in patients that have not

undergone cholecystectomy. It should be diluted in 100 ml of water or fruit juice.[65]

The maximum recommended daily dose of rifampicin is 600 mg. Its effect becomes evident one month after starting the therapy. It has shown efficacy in cases that did not respond to the combination of other medications.

Sertraline, a serotonin reuptake inhibitor, at a daily dose of 75-100 mg has been effective in controlling pruritus, and so is recommend as a first-line alternative, starting at low doses and gradually increasing every 4-5 days.[66]

The recent Fibrates for Itch in Fibrosing Cholangiopathies (FITCH) study on 70 patients with chronic fibrosing cholangiopathies showed that bezafibrate, at a daily dose of 400 mg, was superior to placebo for improving moderate-to-severe pruritus in patients with PBC and PSC.[67]

There are general recommendations and invasive measures[64–66] for refractory pruritus, but with insufficient evidence regarding them. Liver transplantation should be considered in patients that have not responded to previous measures for relieving the pruritus, regardless of the grade of liver disease.

Fatigue. Fatigue is a common complaint of patients with chronic cholestatic disease, presenting in 40-86%,[64,67] and is multifactorial (autonomic dysfunction, metabolic alterations, sleep alterations, and medications).[68] The contributing co-alterations to fatigue, such as hypothyroidism, electrolyte alterations, anemia, kidney damage, diabetes, and medication side effects, should be identified and treated. There is no validated drug therapy for treating those patients, and so the therapeutic recommendations are directed at controlling the factors that potentially contribute to and exacerbate the fatigue. For example, three publications on the role of modafinil in the management of fatigue in patients with PBC suggest that said drug showed no greater benefit, compared with placebo.[64–72]

Osteoporosis. Metabolic bone disease, also known as hepatic osteodystrophy, is a major extrahepatic manifestation related to chronic cholestasis that occurs in up to 60% of patients with said condition, with reports of vertebral fractures, followed by those of the wrist and lower limbs.[73] Its occurrence is multifactorial, and includes vitamin deficiencies, immune system alterations, endocrine alterations, certain medications, and individual characteristics, such as female sex, advanced age, low body mass index, lifestyle, and liver disease progression. Treatment is based on the modification of risk factors, such as smoking, alcohol use, sedentarism (avoided through regular, but low impact, exercise), overweight, falls, etc.[71,72] In addition, a vitamin D supplement should be taken if its daily requirements are not met through diet. Bisphosphonate use is only justified in the presence of frank osteoporosis demonstrated by densitometry, but there is no evidence that it reduces the risk for fractures.[73]

Malnutrition. Malnutrition can be present in up to 40% of patients with chronic cholestatic disease. Even though factors associated with reduced food consumption secondary to the underlying liver condition have been described, such as anorexia, nausea, vomiting, and depression, malnutrition is generally not related to deficient food intake. Its impact can be reflected in muscle mass loss, fatigue, metabolic bone disease, and manifestations due to vitamin deficiencies. A nutritional evaluation should be carried out in patients with chronic cholestatic disease. Even though there are no formal recommendations with respect to malnutrition, the intake of 1-1.5 g/kg/day of protein and the non-protein caloric intake of 25-35 kcal/kg/day are considered reasonable. The deficiency of fat-soluble vitamins (A, D, E, and K) can be a problem and manifestations of such deficiencies should be systematically searched for, to justify the corresponding measures to be taken and treatment.[73]

Coagulation and dyslipidemia. The parenteral administration of vitamin K and its monthly or yearly monitorization should be carried out only in cases of severe coagulopathy secondary to vitamin K deficiency.[73] Supplementation is suggested in jaundiced patients with advanced disease or in those taking rifampicin. With respect to dyslipidemia associated with cholestasis, hypercholesterolemia predominates, and generally occurs in those patients. However, it tends to be associated with an increase in high density lipid (HDL) cholesterol levels and is not associated with an increased risk for cardiovascular disease, thus it is not an indication for lipid-lowering treatment.[73–75]

What is the treatment for intrahepatic cholestasis of pregnancy?

Drug treatment is the basis for improving symptomatology and for normalization of both the mother and fetus. UDCA is the treatment of choice at a dose of 10-15 mg/kg maternal weight/day divided into two takes, albeit up to 20 mg/kg is safe (a category B fetal risk drug). UDCA improves bile acid transport and the excretion of progesterone sulfates, as well as improving bile acid transport from the placenta to the maternal blood. Clinical and biochemical improvement in the pregnant woman has been reported in up to 75% of cases, as well as a decrease in fetal complications.[76–82] UDCA with rifampicin (a category C fetal risk drug) can be used starting from the third trimester, rescuing one-third of the patients that do not respond to UDCA as monotherapy. Rifampicin is a second-line drug but aids in improving symptoms of cholestasis.[83–85] Other studies have shown some clinical improvement in intrahepatic cholestasis of pregnancy with the administration of cholestyramine, dexamethasone, and S-adenosyl-L-methionine.[86–92]

Liver transplantation in patients with cholestatic diseases?

Molecular absorbent r#xeaulating system (MARS) therapy, which removes substances bound to albumin, has been used as bridging treatment to liver transplantation due to intractable pruritus.[93,94]

Liver transplantation is indicated for patients with chronic liver diseases. In the past 10 years, there has been a decrease of approximately 20%, in the number of patients with PBC that require transplantation.[95] Survival in a patient with PBC that requires a transplant is more favorable than with any other etiology of cirrhosis. Patients should be referred to a transplantation center upon presenting with a MELD score above 15, total bilirubin > 6 mg/dl, or a Mayo score above 7.8. Intractable pruritus is also an exceptional indication for liver transplantation.

Chronic fatigue has been ruled out as a justification for liver transplantation.[96] Graft survival at 1, 3, 5, and 10 years is 85, 80, 78.1, and 71.9%, respectively. Patient survival at 1, 3, 5, and 10 years is 90.2, 86.7, 84.4, and 79%, respectively.[97,98] Currently, the most experience in liver transplantation in PBC is found in the study by Montaño-Loza et al.[99] In a total of 785 patients, they reported recurrence in 22% at 5 years and 36% at 10 years, after transplantation. The risk factors for post-transplantation recurrence were age at diagnosis < 50 years, age at transplantation < 60 years, tacrolimus use, and biochemical markers of severe cholestasis.

Osteopenia can worsen within the first 6 months after transplantation, until bone mineral density returns to the baseline values at 12 months and then continues to increase. Replacement therapy is required.[100–102]

PSC is an adequate indication for transplantation, when there is: recurrent bacterial cholangitis, despite medical and endoscopic treatment; decompensated chronic liver disease; and intractable pruritus. Disease recurrence presents in approximately 50% of patients at 5 years, with graft loss in approximately 25%. The diagnosis of PSC recurrence is based on biochemical, radiologic, and histologic data, especially multiple, non-anastomotic bile duct strictures, after ruling out other etiologies, such as secondary ischemia, hepatic artery thrombosis, and infections.[103]

Summary of the approach to the cholestatic patient

Patients very frequently present with jaundice, whose etiology must be determined. Within the initial evaluation, determining the type of bilirubin that is elevated, together with alkaline phosphatase levels, enables the identification of a cholestatic presentation.

If the ALP level is 1.67-times higher than the ULN – confirmed by repeating the liver function tests – and if the GGT level, and occasionally the direct bilirubin level, are elevated, a presentation of cholestasis is confirmed. Abdominal ultrasound is the study of choice for continuing the evaluation of those patients.

When the abdominal ultrasound reveals bile duct dilation, extrahepatic cholestasis is suspected. If the cause of the obstruction (stone, tumor) is also viewed in the ultrasound, a therapeutic procedure, such as ERCP or choledoscopy, can directly be performed. When the choledochus is dilated but the cause of obstruction is not identified, MR cholangiography or CT cholangiography should be carried out to search for the cause of obstruction, and once identified, proceed to a therapeutic intervention.

When there is no identifiable cause of bile duct obstruction or the biliary tree is normal from the start, then cholestasis of intrahepatic etiology is suspected.

Finally, when facing the presenting features of intrahepatic cholestasis, the next step is to evaluate the remaining liver function tests. The aminotransferases are particularly important, given that the elevation of each of them can guide us toward certain diagnostic possibilities. Even the absence of their elevation can be very useful for leading us toward the possible diagnoses.

Conclusions

Cholestatic diseases are highly prevalent worldwide and having guidelines for their adequate approach is imperative. A large number of physicians still confuse the terms cholestasis, jaundice, and hepatitis, resulting in delays in the approach and confusions regarding treatment. Moreover, distinguishing between the presenting features of intrahepatic cholestasis and extrahepatic cholestasis can be challenging, even for the most experienced physicians, thus the knowledge and use of guidelines for ordering the different diagnostic studies and performing the indicated therapeutic maneuvers are indispensable. The present document is the first scientific position statement on the theme developed by the three most important gastroenterology societies in Mexico and aims to function as an aid to the clinical approach of those patients. It also puts forward the different research opportunities that can be taken advantage of in our country, so that in the future, rather than a position statement, guidelines based on the national experience can be developed.

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Conflict of interest

RaÚl Contreras is an advisor for Sanofi and a speaker for Schwabe Pharma and Pfizer.

Graciela Castro is a speaker for Gilead, Abbvie, Abbott, Eisai, Medix, Cellpharma, and GSK.

Eira Cerda is a speaker for Gilead, Abbvie, Takeda, Medix, Bayer, Sanfer, and MSD.

Fátima Higuera is a speaker for Gilead, Takeda, Medix, and Schwabe Pharma.

Ignacio Aiza is a speaker for Gilead, Italmex, and Abbvie.

Laura Cisneros is a speaker for Abbvie, Gilead, and Bristol.

Linda Muñoz is an advisor for Gilead and Cellpharma and a speaker for Gilead, Abbvie, and Cellpharma.

José Marà Remes is an advisor for Chinoin, Takeda, Sanofi, and Medtronic and a speaker forTakeda, Asofarma, Bicodex, Sanfer, and Medtronic.

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