Portopulmonary hypertension and hepatopulmonary syndrome

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The clinically and pathophysiologically distinct entities of portopulmonary hypertension and hepatopulmonary syndrome occur in a substantial proportion of patients who have advanced liver disease of different causes. These disorders are notoriously underdiagnosed, but they have a substantial impact on survival and require focused treatment. Abnormal intrapulmonary vascular dilatation, the hallmark of hepatopulmonary syndrome, can cause profound hypoxaemia that can be very difficult to treat. By contrast, portopulmonary hypertension results from excessive pulmonary vasoconstriction and vascular remodelling that eventually leads to right-heart failure. Insights into the pathogeneses of these syndromes have led to novel therapeutic approaches. However, in severely affected patients, effective treatment remains a difficult task. In selected patients, liver transplantation represents the only treatment option, but the decision to do isolated liver transplantation is particularly challenging in patients who have severe pulmonary disease involvement. Data from several centres have contributed to provide criteria that allow improved prediction of which patients may, or may not, benefit from liver transplantation alone.

Cardiopulmonary abnormalities are present in most patients who have advanced liver disease. A combination of pulmonary and hepatic risk factors can lead to the synchronous existence of liver and lung disease, as seen in combined alcohol, drug, and nicotine consumption. Malnutrition because of advanced cirrhosis can lead to immunosuppression, which puts these patients at risk of infectious pulmonary complications. Most notably, pneumonia accounts for 20–40% of the serious infections encountered in patients with alcohol-related liver disease. Large amounts of ascites or pleural effusions resulting from advanced portal hypertension compromise the lung mechanically, and frequently cause severe dyspnoea. Furthermore, specific diseases affecting the liver and the lung, including α-1 antitrypsin deficiency or cystic fibrosis, alter the function of these organs’ systems in some patients.

Besides these well-recognised disorders, two distinct pulmonary syndromes deserve special attention when dealing with patients with chronic liver disease: portopulmonary hypertension and hepatopulmonary syndrome. These two syndromes seem pathogenetically linked to the presence of portal hypertension, but their pathophysiological mechanisms clearly differ. The development of portopulmonary hypertension or the hepatopulmonary syndrome has major clinical and prognostic implications and requires specific treatment considerations. In this review, we provide a detailed summary of the epidemiology, pathophysiology, diagnosis, and treatment of portopulmonary hypertension and hepatopulmonary syndrome.

Portopulmonary hypertension

Haemodynamically, portopulmonary hypertension is defined by the presence of the following features in patients with portal hypertension: raised pulmonary arterial pressure (mean pressure determined by right-heart catheterisation of >25 mm Hg at rest and >30 mm Hg during exercise); raised pulmonary vascular resistance (>240 dyne s⁻¹ cm⁻⁵) in the presence of a pulmonary arterial occlusion pressure; or a left-ventricular end-diastolic pressure of less than 15 mm Hg. According to the current WHO classification, portopulmonary hypertension is no longer classified as secondary pulmonary hypertension but as pulmonary arterial hypertension associated with liver disease or portal hypertension. Reports on the incidence of pulmonary hypertension in patients with liver disease vary greatly. In autopsy studies, pulmonary vascular changes consistent with the presence of pulmonary hypertension have been reported in 0-7% of patients with cirrhosis. By use of various diagnostic criteria, 2–10% of cirrhotic patients have been estimated in clinical studies to be at risk of developing pulmonary hypertension. In selected patients who have advanced liver disease, especially those assessed or referred for liver transplantation, pulmonary hypertension occurs in up to 16%. Although these observations seem to suggest that portopulmonary hypertension is a complication affecting mainly patients with advanced liver disease, no clear relation between the severity of hepatic dysfunction or raised portal venous pressure and the severity of pulmonary hypertension has been conclusively shown.

Search strategy

We did an unrestricted MEDLINE search with use of the key words “porto-pulmonary hypertension”, “pulmonary hypertension and liver”, “pulmonary hypertension and cirrhosis”, and “hepatopulmonary syndrome”. For papers we deemed relevant for this review, we did a secondary search with the “related-articles” option in MEDLINE. We selected retrieved reports on the basis of their scientific merit and relevance for this review.
The development of severe pulmonary hypertension in patients who have cirrhosis is an ominous prognostic sign. Nevertheless, the reported survival rates vary substantially. In an analysis of 78 patients with portopulmonary hypertension who had a mean pulmonary arterial pressure of 59 mm Hg (SD 19), the median survival was 6 months and the 5-year survival was less than 10%. By contrast, Hervé and colleagues reported an actuarial 5-year survival of 50% in 39 patients with portopulmonary hypertension who had similar haemodynamics.

**Pathogenesis**

The development of portopulmonary hypertension seems to be independent of the cause of portal hypertension. Although most patients with portopulmonary hypertension have cirrhosis as the underlying disease, the syndrome has been described in patients with portal hypertension due to non-hepatic causes, such as portal venous thrombosis in the absence of chronic hepatic disease. Thus, portal hypertension seems to be the required driving force of pulmonary hypertension.

The mechanisms by which portal hypertension causes pulmonary hypertension remain incompletely understood. A hyperdynamic circulation state seems to be present in almost all patients who have portopulmonary hypertension in the early stages of disease. However, high cardiac output and hyperdynamic circulation is a hallmark of almost all patients with advanced liver disease who develop portal hypertension. Several factors are presumed to lead to this feature, including splanchnic volume overload and bowel-wall congestion, leading to the release of endotoxins and cytokines into the splanchnic circulation. High cardiac output in turn delivers an increased amount of shear stress on the pulmonary circulation, which responds in several ways: the maintenance of an adequate pulmonary vascular resistance will prevent development of any syndrome; and abnormal pulmonary vascular dilatation will lead to an abnormally decreased vascular resistance and hepatopulmonary syndrome. By contrast, increased vascular resistance caused by vasoconstriction and progressive pulmonary vascular remodelling due to proliferation of pulmonary arterial endothelial cells and smooth-muscle cells will result in pulmonary hypertension. In these two cases, portopulmonary hypertension and the hepatopulmonary syndrome, changes in vascular resistance are caused partly by variations in the vessel tone but probably more so by pulmonary vascular remodelling.

The presence of a high cardiac output can result in a mild degree of pulmonary hypertension in the presence of a normal or near-normal pulmonary vascular resistance, which might have led to the overestimation of the incidence of portopulmonary hypertension in some case series. The individual factors at the cellular and molecular levels that determine the direction of the outlined vascular response have still to be elucidated but seem to vary in association with the stage of the disease.

Portopulmonary hypertension remains of mild to moderate severity in most patients, and vasoconstriction and medial hypertrophy of the pulmonary arteries are the dominant features of pulmonary hypertension. However, in an unknown proportion of patients, mild or moderate portopulmonary hypertension progresses to severe disease, and becomes a clinically apparent complication in chronic liver disease or portal hypertension. Histologically, proliferative pulmonary arteriopathy with obliteration of the vessel lumen by endothelial cells and smooth-muscle cells and with formation of plexiform lesions indistinguishable from those seen in primary pulmonary hypertension is the hallmark of this disorder (figure 1).

In contrast to patients who have mild to moderate pulmonary hypertension, those who progress might show rapid clinical worsening that leads to right-heart failure. The factors involved in the development of proliferative vasculopathy have yet to be identified. One such candidate might be mutations in the bone morphogenetic protein receptor type 2, a member of the transforming growth factor receptor family, which has been linked to proliferative pulmonary vasculopathy and has been detected in patients with familial and sporadic primary pulmonary hypertension, but has not yet been described in patients with portopulmonary hypertension. Mutations in ALK-1, another member of the transforming growth factor receptor family, have been linked specifically to pulmonary hypertension in patients with hereditary haemorrhagic telangiectasia. Other, as yet unidentified, genetic factors are also likely to contribute to the development of proliferative pulmonary vasculopathy in patients with severe portopulmonary hypertension since the underlying pathophysiological abnormalities are present in almost all patients and only a few develop pulmonary hypertension.

**Symptoms and diagnosis**

The most common presenting symptom in patients with pulmonary hypertension, irrespective of its cause, is progressive dyspnoea on exertion. Other symptoms such as fatigue, palpitations, syncope, or chest pain are less frequent. Physical findings indicating pulmonary hypertension are generally subtle and may be completely absent. The most common findings are an accentuated pulmonary component of the second heart sound and a systolic murmur, indicating tricuspid regurgitation. Extended jugular veins, oedema, and ascites can be signs of either decompensated cirrhosis or overt right-heart failure.

The diagnosis of portopulmonary hypertension requires raised pulmonary arterial pressure and resistance combined with the exclusion of other causes of pulmonary hypertension. Electrocardiography, radiography, or pulmonary-function testing can provide some clues as to...
the presence of pulmonary hypertension, but in most cases, echocardiography provides the first, and mostly accurate, sign leading to the diagnosis. If uncertainty remains, pulmonary hypertension can be conclusively shown—or ruled out—by right-heart catheterisation. The presence of pulmonary hypertension in a patient with cirrhosis and portal hypertension per se is not sufficient to establish the diagnosis of portopulmonary hypertension. Other common causes of pulmonary hypertension, especially left-heart disease, valvular heart disease, interstitial or obstructive lung disease, sleep-related breathing disorders, and chronic thromboembolism, must be excluded first.

When the diagnosis of portopulmonary hypertension has been established, differentiation between mild, moderate, and severe pulmonary arterial hypertension is helpful for prognostic and treatment considerations. There is no universally accepted definition on which this distinction is routinely based, but for practical use cardiac output is better suited for classification than the magnitude of pulmonary arterial pressure. In mild to moderate portopulmonary hypertension, normal or high cardiac output is present and the pulmonary vascular resistance is only slightly raised. However, in severe portopulmonary hypertension cardiac output is reduced and pulmonary vascular resistance is strikingly raised (table).

Management

Patients who have mild portopulmonary hypertension frequently have no symptoms and signs of pulmonary vascular disease. In these patients, specific treatment of pulmonary hypertension is not generally required. However, regular follow-up examinations, including biannual to annual echocardiographic examinations, are advisable to monitor the potential progression of pulmonary disease. Even mild to moderate portopulmonary hypertension can pose a notable threat to patients in special situations, such as those in whom major surgery is necessary. The attending physicians for such patients should be experienced in the management of liver disease, accompanying risk factors, continuing drug use.

Anticoagulation

Anticoagulation is recommended in patients who have primary pulmonary hypertension because it can slow disease progression. Efficacy and safety of oral anticoagulants in patients with portopulmonary hypertension have not yet been assessed in trials. Many such patients do not receive anticoagulants because of an increased risk of haemorrhagic complications, especially if there is a history of bleeding from oesophageal or gastric varices. In addition, the failure of liver synthesis leads to low concentrations of coagulation factors and to abnormal global coagulation studies. In such patients the intrinsic anticoagulation secondary to hepatic synthetic failure may render anticoagulation in principle expendable. However, from the limited data available, whether anticoagulation should be recommended for patients with severe portopulmonary hypertension is impossible to judge.

Pharmacotherapy

Intravenous epoprostenol is the best-studied drug in patients with portopulmonary hypertension. Although the efficacy and safety of epoprostenol in such patients has never been addressed in randomised controlled trials, strong evidence from several open-label studies shows that this drug given intravenously improves haemodynamics and exercise capacity in patients with portopulmonary hypertension. However, preliminary data from the Mayo Clinic suggest that intravenous epoprostenol does not improve long-term survival. This treatment option has major drawbacks. Continuous intravenous epoprostenol administration requires permanent central venous access and uninterrupted infusion of the drug. Central venous access and the delivery system are prone to serious complications resulting from infection or pump failure. Therefore, patients must adhere strictly to the recommendations for treatment and handling of the delivery system. For these reasons, continuous intravenous epoprostenol treatment should not be used in patients with continuing excessive alcohol intake or illicit drug use.

Other prostanooids have become available for the treatment of pulmonary arterial hypertension that can be administered orally, subcutaneously, by inhalation, and, therefore, have a more favourable safety profile than intravenous epoprostenol. However, experience with aerosolised iloprost, oral beraprost sodium, or treprostinil in portopulmonary hypertension is still anecdotal and large trials assessing their safety and efficacy for this indication are needed.

The endothelin system might be a potential target in portopulmonary hypertension. Plasma endothelin-1 concentrations are substantially higher in patients with portopulmonary hypertension than in healthy controls and patients with cirrhosis but no pulmonary hypertension. The dual endothelin-receptor antagonist bosentan can be administered orally and has beneficial effects on haemodynamics and exercise capacity in patients with pulmonary hypertension because it can slow...
primary pulmonary hypertension and pulmonary arterial hypertension associated with systemic sclerosis. Patients with liver disease were excluded from the initial clinical trials because of safety concerns about the hepatotoxic potential of bosentan and other endothelin-receptor antagonists under clinical investigation. A rise in aminotransferase activity is seen in 10–15% of patients receiving bosentan. A mechanism by which bosentan might cause liver injury is impairment of the activity of bile-salt transporters, leading to hepatocellular bile-salt accumulation. Whether additional as yet unidentified mechanisms also contribute to liver toxic effects is unclear.

So far, no case of severe liver injury has been associated with bosentan use. However, two cases of severe liver injury, one of them fatal, have been associated with sitaxsentan, a novel selective inhibitor of type-A endothelin receptors. Despite the shortage of controlled data, approval of bosentan by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products includes patients with portopulmonary hypertension, provided liver function is not severely impaired (Child-Pugh classes B and C). Preliminary unpublished experiences from several centres suggest that bosentan is safe and effective in selected patients with portopulmonary hypertension, but a high degree of caution is prudent in this group of patients until further investigations have addressed the safety and efficacy of this approach. For the time being, the use of bosentan in patients with portopulmonary hypertension should be restricted to highly experienced centres.

Sildenafil, a phosphodiesterase-5 inhibitor, is another novel and promising substance for the treatment of pulmonary hypertension, but controlled data and reported experiences in patients with portopulmonary hypertension are not yet available.

Liver transplantation

Liver transplantation requires special consideration, and is likely to be beneficial only in a selected cohort of patients with portopulmonary hypertension. The presence of pulmonary hypertension of any severity increases the perioperative and long-term risks of liver transplantation. Clinical assessment protocols before liver transplantation should, therefore, specifically include a screening algorithm for portopulmonary hypertension in suspected cases, as outlined above. In addition, patients with proven portopulmonary hypertension are better managed in transplant centres that have specific experience with this complication of advanced liver disease. Given this approach, liver transplantation generally has a good outcome in patients with mild to moderate portopulmonary hypertension.

Mild to moderate pulmonary hypertension, signified by a high cardiac output in cirrhotic patients, is frequently reversible after liver transplantation, but severe pulmonary hypertension is not and has been associated with high mortality after this intervention. In such patients, specific pulmonary vasodilator treatment followed by liver transplantation might be necessary to improve transplant outcome. Severe portopulmonary hypertension poses a pulmonary risk for liver-transplant candidates but also leads to a compromised perfusion of the liver graft. After liver-transplantation, congestion of the hepatic veins due to decreased right-ventricular function carries a notable risk of primary graft dysfunction. In highly selected cases, combined liver and lung transplantation or even heart-lung-liver transplantation might have to be considered.

Hepatopulmonary syndrome

The reported frequency of hepatopulmonary syndrome in patients with liver disease is between 4% and 29%. The differing incidence is primarily due to heterogeneity of the applied diagnostic criteria. This syndrome is a well-defined cause of hypoxaemia in patients who have liver disease due to abnormal intrapulmonary vascular dilatation, which results in an excess perfusion for a given state of ventilation. This complication is characterised by anatomical shunting and a diffusion-perfusion abnormality (figure 2). Thus, abnormal pulmonary vascular dilatation plays a central part in the hepatopulmonary syndrome, whereas abnormal vasoconstriction and obliterator vascular remodelling are the key features of portopulmonary hypertension. In fact, in one case report, development of portopulmonary hypertension in a patient who originally had hepatopulmonary syndrome seemed to lead to the correction of hypoxaemia.

As with portopulmonary hypertension, hepatopulmonary syndrome occurs mostly in patients who have established cirrhosis and portal hypertension. The association between the severity of liver disease and the degree of hypoxaemia is slight, but the risk seems to be highest in Child C patients. The cause of liver disease leading to portal hypertension does not seem to affect the development of the hepatopulmonary syndrome, which is evident from reports of a hepatopulmonary syndrome in patients with prehepatic portal hypertension in the absence of chronic liver disease, and even in patients with acute or chronic inflammatory liver disease without evidence of cirrhosis or portal hypertension.

The prognosis of the hepatopulmonary syndrome is poor and mortality rates of 41% within a mean observation period of 2·5 years have been reported.

Pathogenesis

From a pathophysiological point of view, hepatopulmonary syndrome is almost exactly the opposite
of portopulmonary hypertension. Evidence is growing rapidly that abnormal intrapulmonary vascular dilatation is linked to portal hypertension, which in itself leads to altered bowel perfusion and an increased rate of enteral translocation of gram-negative bacteria and endotoxin. This process in turn stimulates the release of vasoactive mediators, which include tumour necrosis factor α, haem-oxygenase-derived carbon monoxide, and nitric oxide. Experimental and clinical data suggest that increased production of nitric oxide in the lung plays a central part in the pathogenesis of the hepatopulmonary syndrome. Increased concentrations of exhaled nitric oxide are positively correlated with the increase of alveoloarterial oxygen difference. The constitutive and the inducible isoforms of nitric-oxide synthase have been implicated in this process. In addition, the endothelin system, especially abnormal activation and increased expression of endothelial type B endothelin receptors, has been implicated in the pathogenesis of the hepatopulmonary syndrome. In patients who have pulmonary hypertension, endothelin predominantly exerts vasoconstrictive and mitogenic effects due to activation of type A and type B endothelin receptors on pulmonary arterial smooth-muscle cells. By contrast, in experimental models of the hepatopulmonary syndrome, the expression of endothelial type B endothelin receptors is strikingly increased and is linked to the increased production of nitric oxide by endothelial cells (figure 3). Histological examination reveals dilated intrapulmonary arterioles and capillaries and dilated vascular channels between pulmonary arteries and veins. The latter structures have been described as vascular spider naevi on the pleura and exhibit features of vasoculogenisis. A typical, albeit not universal, finding in hepatopulmonary syndrome is orthodeoxia—ie, arterial deoxygenation improving in recumbency—which leads to the debilitating clinical symptom of orthodeoxia-platynoea (hypoxaemia and dyspnoea induced or worsened in the upright position). This phenomenon is explained by the worsening of diffusion-perfusion matching and an increase of the shunt fraction in the upright position because of increased perfusion of the lower lobes.

**Symptoms and diagnosis**

Patients with hepatopulmonary syndrome complain of progressive dyspnoea and can become increasingly cyanotic. Some patients develop clubbing, and cutaneous telangiectasias (spider angiomas) are typically seen in high numbers. In some instances, systemic arteriovenous shunting causing severe complications such as stroke, cerebral haemorrhage or brain abscess may occur. Physical examination might reveal evidence of liver disease, but findings in the lungs and the heart are generally normal unless coexisting disease is present. The condition of many patients who have hepatopulmonary syndrome rapidly worsens even in the presence of stable hepatic synthesis, detoxification function, and degree of portal hypertension. Since hypoxaemia is a prerequisite of the fully established hepatopulmonary syndrome, every diagnostic approach should begin with the documentation of hypoxaemia at rest by means of arterial or capillary blood-gas analysis. An arterial partial pressure of oxygen lower than 8·65 kPa is a good cut off to show a decreased value. Histological examination reveals dilated intrapulmonary arterioles and capillaries and dilated vascular channels between pulmonary arteries and veins. The latter structures have been described as vascular spider naevi on the pleura and exhibit features of vasoculogenisis. A typical, albeit not universal, finding in hepatopulmonary syndrome is orthodeoxia—ie, arterial deoxygenation improving in recumbency—which leads to the debilitating clinical symptom of orthodeoxia-platynoea (hypoxaemia and dyspnoea induced or worsened in the upright position). This phenomenon is explained by the worsening of diffusion-perfusion matching and an increase of the shunt fraction in the upright position because of increased perfusion of the lower lobes.

**Figure 3: Schematic Illustrating Hypothesis Underlying Pulmonary-Vessel Dilatation in Hepatopulmonary Syndrome**

Figure 3: Schematic illustrating hypothesis underlying pulmonary-vessel dilatation in hepatopulmonary syndrome. NO=nitric oxide, eNOS=endothelial nitric oxide synthase. Left panel: In absence of cirrhosis and portal hypertension, endothelin-1 is secreted, mainly abluminally, where it activates vasoconstrictive endothelin type A receptors on smooth-muscle cells and contributes to maintenance of adequate vascular tone. Under physiological conditions, luminally secreted endothelin is rapidly cleared from circulation after binding to endothelial type B endothelin receptors, which stimulates production of NO, partly antagonising vasoconstrictive effects of endothelin. Right panel: in presence of portal hypertension, hepatic production occurs of endothelin-1 and expression of endothelial type B receptors, but no type A receptors increase in pulmonary vasculature. Signalling via endothelially expressed endothelin B receptor leads to increased NO production by eNOS, with the overall effect of pulmonary vascular dilatation, which is pathognomonic of hepatopulmonary syndrome.
typical of the hepatopulmonary syndrome are present. However, an immediate appearance of echo contrast material in the left atrium suggests the presence of a cardiac right-to-left shunt that is an important differential diagnosis. An alternative to contrast echocardiography is scintigraphic perfusion scanning. Under normal conditions, Tc albumin macroaggregates that exceed 20 μm in diameter are almost completely trapped in the pulmonary circulation. In the presence of a cardiac right-to-left shunt or intrapulmonary vascular dilatation the uptake of Tc macroaggregated albumin can be documented in other organs such as the brain or the spleen. This technique has been used for the diagnosis of hepatopulmonary syndrome and for the quantification of the magnitude of shunting.

Pulmonary angiography is not a standard diagnostic tool in patients who have hepatopulmonary syndrome. However, in patients with a poor response to oxygen administration, which suggests substantial right-to-left shunting, pulmonary angiography can be done to identify focal arteriovenous malformations that may be amenable to embolisation.

Management

The treatment of hepatopulmonary syndrome includes the correction of hypoxaemia by administration of oxygen. However, in severe cases and the presence of right-to-left shunting, hypoxaemia might not be fully correctable.

Theoretically, the ideal treatment of hepatopulmonary syndrome would consist of a drug or any other means to reverse of intrapulmonary vascular dilatation. Unfortunately, this therapeutic goal cannot be fully achieved in most patients with the currently available treatments. Increased production of nitric oxide is a potential target, but this approach has not been established as routine. Diets containing low amounts of L-arginine, the substrate of nitric oxide synthase, have been developed.

The focus is, therefore, on strategies aimed at improving the stability of the pulmonary circulation. Reduction of the portal venous pressure, such as β-adrenergic-receptor blockers and nitrates, which constitute the standard of care in chronic portal hypertension, exert no beneficial effect on oxygenation in patients with hepatopulmonary syndrome.

Novel treatment options are being explored and include antibiotics that aim to reduce enteral bacteria translocation. Experimental models in common-bile-duct-ligated rats suggest that the use of antibiotics to decrease bacterial translocation in the bowel is effective in preventing the development of hepatopulmonary syndrome, but whether this approach has reproducible and long-standing clinical effects remains to be shown.

In patients with progressive and refractory hypoxaemia, liver transplantation is the treatment of choice since it can correct all the discussed abnormalities secondary to the correction of the underlying hepatic disease. Severe hypoxaemia is a strong risk factor for increased mortality after liver transplantation but complete resolution after this procedure is well documented. Improvement in oxygenation might, however, take several months or even years.

Future perspectives

Although portopulmonary hypertension and the hepatopulmonary syndrome are associated with the same underlying diseases, they have distinct pathophysiological backgrounds. The rapidly increasing knowledge of pulmonary vascular tone regulation and vascular remodelling, including the identification of genes that increase the risk of developing pulmonary vascular disease, will eventually lead to a specifically targeted treatment approach. The treatment of portopulmonary hypertension has been largely based on the latest advances in the treatment of other forms of pulmonary arterial hypertension, but studies are now needed that are tailored specifically to analyse specifically patients who have portopulmonary hypertension. This requirement is particularly true for new substances such as endothelin-receptor antagonists and phosphodiesterase inhibitors. For theoretical reasons, endothelin-receptor antagonists, especially those which specifically block type B endothelin receptors, might also be useful in hepatopulmonary syndrome, but this remains to be studied. The same is true for various selective inhibitors of nitric-oxide-synthase isoforms, which are currently being developed.

Experiences with liver transplantation teach us that the hepatopulmonary syndrome is completely reversible in most patients, which opens one currently available perspective for successful treatment.

Conflict of interest statement

M H Hooper has served as consultant for and has received speaker’s fees from Schering, Pfizer, and Actelion, who produce substances that are mentioned in the paper. C P Strasburg and M J Kroopka have no personal or financial relationship to report that causes a conflict of interest in writing this review.

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