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ence what is found. Databases of adverse reactions and types of publications that were excluded from the review should also be considered, as the *Handbook for Systematic Reviews of Interventions* now recommends. The Cochrane review of melatonin for jet lag did this.⁵ It found hints of a possible interaction with warfarin and a suggestion of harm in children with severe epilepsy⁶; both these problems remain to be investigated.

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Clinical course of infection with hepatitis C

Is still poorly understood

Although around 170 million people worldwide are currently infected with hepatitis C virus (HCV), its course is still not well understood. Predicting the course of infection is essential to deciding who and when to treat with the powerful available drugs—pegylated interferons and ribavirin—and anticipating the need for liver transplants and other interventions for end stage liver disease.

Several factors influence the clinical course of HCV infection. Being older than 40 at the time of infection, male sex, coinfection with hepatitis B virus or HIV, steatohepatitis, immunosuppression, and predisposing human leukocyte antigen (HLA) haplotypes have all been associated with progression of fibrosis and possible development of cirrhosis. The main risk factor for faster progression to cirrhosis in HCV infection remains, however, the consumption of alcohol.^{1,2} Moreover, many intravenous drug users, the main population still at risk of HCV infection in developed countries, consume alcohol regularly.

Despite this evidence about risk factors, studies of the course of HCV infection have so far led to conflicting conclusions, and the two most recent studies are no exceptions. Wiese et al extended the follow-up of a cohort of 1980 women infected in the former East Germany from a single source (anti-D immunoglobulin contaminated by HCV genotype 1b) in 1978 and 1979 and found that, after 25 years, only 48% of untreated women still had HCV RNA in their blood. Of those untreated women who developed chronic hepatitis C, 1.3% had cirrhosis, 4.4% had marked hepatic fibrosis, and 0.1% had hepatocellular carcinoma.³ Liver associated mortality was 0.5% in viraemic women (half of them had serious comorbidities).

Another recent study gives an entirely different picture of prognosis. D'Souza et al studied 206 first generation and second generation adult Asian immigrants to northeast London who were, according to history and extrapolation of linear regression analyses, most probably infected with HCV in childhood or by the age of 20. The investigators selected 143 patients for analysis and compared them with 239 white patients. Liver biopsies showed cirrhosis in 11% of Asians aged 26-40, 33% of those aged 41-60, and 78% of those older than 60.⁴ Although only 25% of white patients aged 61-80 had

cirrhosis, on the basis of multivariable linear analysis the authors concluded that prolonged infection for over 50 years leads to cirrhosis in most patients in other populations too. Can we then conclude that white European women are almost immune from cirrhosis induced by HCV, whereas the prognosis is very poor for Asians likely to be infected in childhood? We cannot.

The clinic based, cross sectional study by D'Souza et al looked at a highly selected group of individuals who were ascertained because they had HCV infection. Prone to detection bias and largely depending on extrapolation of regression lines, the study overestimates the risk of cirrhosis and reports the highest rate ever recorded for any such population of patients. Still, the data by D'Souza et al confirm that people can survive for more than 60 years with HCV infection, even when they have developed cirrhosis.

How should we put into context these two conflicting reports? Studies of the clinical course of HCV infection transmitted vertically or acquired early in life clearly show that progression of the disease is usually very slow, at least in the first three decades of life.⁵ The study by D'Souza et al is therefore exceptional in showing rapid progression in 11% of patients aged under 40.⁴ On the other hand, cohort studies with long term follow-up of people who acquired HCV in adulthood⁶ confirm and extend in time the data of Wiese et al.³ Finally, although the progression of hepatic fibrosis in hepatitis C seems to be non-linear,⁷ and the virus seems to be more fibrogenic in older people,⁸ population based studies show that infection with HCV is highly prevalent in asymptomatic people who live to old age.^{9,10} Overall, the study by D'Souza et al adds little to our knowledge of the course of HCV infection. The cohort study by Wiese et al is more robust, but it may underestimate the occurrence and progression of liver disease because it is confined to young, healthy women, who are already at reduced risk of liver disease related to HCV. Most low income countries cannot afford antiviral drugs. Worldwide, antiviral treatment for HCV infection is therefore underused, and treatment does not have a marked impact on the course of this infection in populations.¹¹ We should urgently aim to reduce the spread of HCV infection by strictly avoiding reuse of syringes and needles (still practised in many poor countries), and to

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limit the main cofactor of disease progression through well designed public health campaigns and interventions capable of reducing alcohol intake. In addition, measures should be taken to reach people in prisons and intravenous drug addicts, still at high risk for disease acquisition and spread. At the same time, researchers and epidemiologists should continue to study the clinical course of HCV infection in those countries where the disease is still actively spreading in the general population.¹²

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Surgery for emphysema

New endoscopic techniques show promise

Emphysema affects 3.1 million people in the United States alone and causes severe disability and early death in up to 45% of patients.¹ Emphysematous destruction of the lung is associated with decreased elastic recoil pressure. As a result, the diseased lung requires less pressure than a normal lung to inflate and, once inflated, exerts less pressure to empty; lungs in emphysema therefore tend to remain inflated, with overexpansion of the rib cage and flattening of the diaphragm. Patients are trapped in a state of permanent hyperinflation and dyspnoea. No amount of effort can empty their lungs: the harder they strain to breathe, the more the airways collapse and obstruct the outflow of gas.

Current medical treatment with inhaled bronchodilators, glucocorticoids, mucolytics, and antioxidants may improve symptoms temporarily but does not prevent the decline in lung function. Various surgical procedures have been implemented in the past to relieve dyspnoea and improve quality of life for such patients.^{w1} Early results of surgery were often encouraging, but surgery rarely achieved sustained objective functional improvement and most of those procedures were gradually abandoned.

Bullectomy is the only operation that has stood the test of time. It allows re-expansion of restricted but potentially functional adjacent lung tissue,² contributes to increased compliance and airway calibre, improves the ventilation-perfusion ratio (V/Q), and decreases the physiological dead space in the lung. Newer surgical procedures such as lung transplantation and lung volume reduction are now established procedures for selected patients, and endoscopic airway bypass and bronchoscopic lung volume reduction show promise.

International guidelines recommend lung transplantation as a viable option for a selected group of patients with end stage chronic obstructive pulmonary disease (COPD)—with forced expiratory volume (FEV₁) that is 25% lower than predicted, resting hypoxia, hypercapnia, secondary pulmonary hypertension, and a deteriorating clinical course.^{w2} Transplantation can produce excellent functional results and improve quality of life.^{w3} Patients with emphysema are ideal candidates for lung transplants because they experience a relatively slow functional deterioration and can tolerate a long wait for a suitable organ. They have enormous chest cavities, rarely suffer adhesions, and rarely have pulmonary hypertension. About 30% of all lung transplants are done for patients with chronic obstructive pulmonary disease,^{w1} and they have better postoperative outcomes than patients with other diseases such as pulmonary fibrosis or primary pulmonary hypertension.^{w3}

The choice of single versus bilateral transplantation in patients with emphysema remains controversial. Younger patients and those with giant bullae or bronchiectasis should be considered for bilateral transplantation to improve lung function and increase life expectancy and to avoid potential complications associated with having one remaining diseased lung. But bilateral transplantation reduces the potential for organ sharing and diminishes the already limited pool of donor organs. Moreover, chronic rejection due to obliterative bronchiolitis affects most patients within as little as five years after surgery, limiting long term survival substantially.³



References w1-w4 are on bmj.com