a)

Numbers/Scenarios	Concepts
Millions	Patients world wide estimated to be affected by a form of CLD
25-30%	Patients affected by CLD expected to develop significant fibrosis and eventually cirrhosis
1st	Liver cirrhosis is, among disease of the GI tract, the most common non-neoplastic cause of death in Europe an USA
7th	Overall cirrhosis ranking within the most frequent causes of death in western countries
variable	Occurence of primary liver cancer (HCC) on cirrhosis, depending on aetiology (most common for viral aetiology HBV or HCV)
peak of incidence of CLDs	Predicted for the next decade together with a shortage of organ donation for OLT
10-15 years	Mean estimated time required for fibrotic progression towards cirrhosis; highly affected by individual factors and aetiology

b)

- male gender
- age at infection (mainly for HCV)
- daily alcohol intake
- obesity and diabetes mellitus
- hepatic iron content
- individual factors leading to differences in: - immune response vs infection agents and related auto-antigens
  - drug metabolism

c)

Bridging fibrosis, a pattern of ECM deposition and septa formation, seen mainly in the liver of patients with HBV or HCV chronic hepatitis, that results from portal-central bridging necrosis and lead mainly to the formation of portal-central fibrotic septa, apparently bridging portal areas with the area of central vein. This pattern, typically associated with interface hepatitis, can lead also to the development of septa bridging portal areas (portal – portal septa) and of blind septa in the parenchyma. Fibrotic septa will also lead to obliteration of central veins and early changes in vascular architecture and connections with the portal system, favouring the development of portal hypertension. Chronic wound healing is the main pathogenetic mechanism driving this pattern of fibrosis progression and MFs involved can be either derived from HSCs, portal fibroblasts or even from bone marrow stem cells (see later). ROS have also been described to concur to pathogenesis.

Perisinusoidal/pericellular fibrosis. This pattern predominates in CLD having alcoholic aetiology (ASH or alcoholic steatohepatitis) or in those conditions of metabolic derangement progressing from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). Here, excess deposition of ECM components in the space of Disse leads to the characteristic “chicken-wire” pattern and is mainly due to HSC/MFs (MFs derived from activation of HSCs); moreover, generation of ROS and oxidative stress predominate as main pathogenic mechanism.

Biliary fibrosis. This definition refers to a rather unique condition, usually seen in diseases affecting the biliary tree, in which there is a concomitant proliferation of reactive bile ductules and periductular MFs (here mainly derived from periportal fibroblasts) leading to formation of portal – portal septa that for long time do not affect significantly vascular connections with portal system. For this pattern, significant alterations in the interactions between epithelial cells (i.e., biliary epithelial cells or BEC) and mesenchymal cells have been proposed as relevant in the pathogenesis together again with ROS and oxidative stress.

Centrilobular fibrosis. This pattern is typically recognized in patients affected by chronic heart failure in which a significant alteration of venous outflow is realized; fibrotic septa develop between central vein areas (central – central septa) and lead to the scenario often defined as of “reversed lobulation”.