Bilirubin is a yellow breakdown product of haem with contradictory properties. In low concentrations (unconjugated) bilirubin is an antioxidant, but in high concentrations it is very toxic for our braincells. Accumulation of (unconjugated) bilirubin in our body can lead to permanent brain damage. Unconjugated hyperbilirubinemia (the accumulation of bilirubin in the blood) is mainly seen in patients with Crigler Najjar disease and in preterm neonates. The standard treatment of unconjugated hyperbilirubinemia is phototherapy: the radiation of the skin with blue light. Although phototherapy is relatively safe, it is not always effective. Patients with Crigler Najjar disease have a life-long (inherited) form of unconjugated hyperbilirubinemia, and need up to 16 hours a day of treatment with phototherapy. Unfortunately, about 25% of these patients develops brain damage despite this intensive treatment regimen. Also in newborns there is still a change of developing brain damage when bilirubin levels are extremely high. In this thesis we have examined new diagnostic and therapeutic options to prevent brain damage. We show that the combination therapy of phototherapy and albumin can prevent the accumulation of bilirubin in the brain of Gunn rats, an animal model for unconjugated hyperbilirubinemia. Next, in our animal model we have shown that an exchange transfusion, a final "rescue treatment" when bilirubin levels are extremely high and fail to respond to phototherapy, is the most effective treatment to establish a rapid decrease in plasma bilirubin levels. As a follow-up treatment, again the combination of phototherapy and albumin is the most effective option in maintaining this hypobilirubinemic effect. With functional diagnostic tests (so called “Brainstem Auditory Evoked Potentials”) we demonstrated in Gunn rat pups that albumin administration can prevent hearing loss. Also, we were able to develop a successful preventive strategy: enteral treatment with polyethylene glycol and ursodeoxycholic acid prevented the hyperbilirubinemic peak in Gunn rat pups shortly after birth. Finally, in a patient study with premature neonates we showed that there is little added advantage by using the bilirubin/albumin ratio compared to total serum bilirubin alone for estimating free bilirubin. The new strategies may ultimately serve as an alternative or additional option for routine treatment, and may prevent bilirubin-induced brain damage in hyperbilirubinemic patients. Accordingly, we think that our results can be used as a starting point for the development of clinical trials in Crigler Najjar patients and in neonates with severe unconjugated hyperbilirubinemia.