Endoscopic Stenting for Palliation of Malignant Biliary Obstruction
A Review of Progress in the Last 15 Years

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Since the late 1970s, endoscopic biliary stenting has become a standard palliative treatment for obstructive jaundice due to malignancies of the pancreas and the hepatobiliary system. Despite the high initial success rate in achieving biliary drainage, endoscopic stenting therapy has been limited by the clogging of biliary stents, usually after four to five months, due to formation of adherent bacterial biofilm and accumulation of biliary sludge. Various methods for the prevention of bacterial adhesion and prolongation of stent patency have been investigated, including prophylactic antimicrobial agents and bile salts, new stent materials, and new stent designs. Recently, the introduction of self-expandable metal stents has significantly improved the duration of stent patency but the cost is considerably higher. Each method has its own merits as well as specific problems. This article reviews the pathogenesis of biofilm formation on the biliary stents and the latest status of research in avoiding stent occlusion.

KEY WORDS: biliary stents; clogging; bacterial biofilm.

The first endoscopic transpapillary insertion of biliary stents was performed in 1979 (1). This procedure quickly becomes a standard method of palliation for pancreaticobiliary malignancies causing obstructive jaundice (2, 3). The success rate for endoscopic stenting exceeds 90% and procedure-related complications are rare (2-4). When endoscopic stenting is compared with bypass surgery for unresectable tumors, the two modes of treatment provide comparable median survival and quality of life is similar (5). As it does not involve puncturing the liver, endoscopic stenting is often preferred to percutaneous transhepatic stenting (6). Unfortunately, the plastic stents in current use tend to clog as a result of bacterial biofilm formation on the stent and of biliary sludge (7, 8). The patients develop recurrent jaundice, fever, and cholangitis. The median patency interval for a 10-Fr stent is only about four to five months (2-4). Stents can be easily replaced, but this is only a temporary solution as replacement stents clog even faster than the first stent. The clogging of biliary stents is a serious limitation for biliary stenting.

SOURCE OF BACTERIA INVADING THE BILIARY TRACT

The biliary tract of a healthy individual does not harbor any microorganisms (9, 10). The sphincter of Oddi acts as an effective mechanical barrier to bacterial invasion from the duodenum (11). A daily bile flow of 800–1000 cc keeps the system flushing, and continuous shedding of mucus from the biliary mucosa helps to prevent bacterial colonization. Nevertheless, there are still transient excursions of bacteria through the biliary system. This was demonstrated in our animal experiment in which a foreign body was
The implant provides a favorable niche for bacterial invasion of the biliary tract via two possible routes. The first is surgical implantation into the gallbladder and bacterial biofilm was found after a short period of time (12). The implant provides a favorable niche for bacterial adhesion and proliferation, thus trapping any bacteria passing through the biliary tract. Microorganisms invade the biliary tract via two possible routes. The first one is hematogenous. Bacteria from the lower gastrointestinal tract can enter the biliary system via the portal circulation (13). The entry of bacteria via this hematogenous route is also facilitated by an elevated intrabiliary pressure associated with obstructive jaundice, as shown in animal experiments (13). On the other hand, in patients who had surgical sphincterotomy or endoscopic stenting, the sphincter of Oddi is disrupted and duodenal–biliary reflux leads to ascending colonization of the biliary system (14–16).

FORMATION OF BACTERIAL BIOFILM RESULTS IN STENT CLOGGING

A clogged biliary stent contains sludgy material with a high protein content. Under electron microscopy, this sludge is composed of microcolonies of bacteria admixed with deconjugated bilirubin, protein, and amorphous substances (7, 8, 17). Based on the morphological similarities between the sludge material causing stent clogging and brown pigment biliary stones, we hypothesized that the two conditions have a similar pathogenetic mechanism (18). Elaboration of bacterial β-glucuronidase and phospholipase by biliary pathogens lead to deconjugation of bilirubin–diglucuronide and lecithin in the bile, hence precipitating calcium bilirubinate and calcium salts of fatty acids. With time, the growth of biofilm and progressive agglomeration of the bile sediment forms biliary sludge, which results in occlusion of the stent lumen. The first step in the pathogenesis of stent occlusion is bacterial adhesion on the stent surface. Groen et al have reported a layer of protein covering the surface of the stent as a surface conditioning protein for bacterial adhesion (19). However, the origin of this protein is unknown and its chemical nature remains to be elucidated. At least two groups of workers have reported that defects in the manufacturing of biliary stents, such as an irregular inner surface and badly constructed side holes, could facilitate bacterial colonization (20, 21). New stent materials and different designs of the stents have thus been put forward (see below).

ANTIBIOTICS AND OTHER ANTIMICROBIAL AGENTS

As clogging of the biliary stents is a result of bacterial colonization and biofilm formation, it is logical to keep the biliary tract "sterile," with antimicrobial agents as the first attempt to avoid stent clogging. The earliest report was to give aspirin (to reduce mucin secretion) and doxycycline (to suppress bacterial growth) to a group of 60 patients who needed biliary stenting (22). Unfortunately, doxycycline was not the right antibiotic to test since most biliary pathogens are gram-negative coliforms. The high patient dropout rate and the short follow-up of that study has also contributed to its failure to confirm the benefit of antimicrobial treatment. Recently, Libby et al added a subbactericidal dose of ciprofloxacin to infected bile and demonstrated that bacterial adherence to polyethylene stent was significantly reduced in vitro (23). The decreased bacterial adherence was attributed to the change of bacterial surface characteristics. In an animal study, the same group has also shown that ciprofloxacin treatment alone has significantly prolonged the stent patency (24). The question is: can the benefits of prophylactic antibiotic treatment in animal studies be translated into clinical benefit? Ghosh and Palmer used a cyclical antibiotics regimen (composed of ampicillin, metronidazole, and ciprofloxacin) together with ursodeoxycholic acid (a choleretic agent) and the result was disappointing (25). In their study, however, antibiotics and ursodeoxycholate were commenced only at two weeks after endoscopic stenting. Interestingly, a similar study using ursodeoxycholic acid plus norfloxacin (for selective intestinal decontamination) has shown a dramatic improvement in stent survival from six to 49 weeks (26). Although the untreated group in this study has a surprisingly short median duration of patency, the difference between the two groups is very impressive. The discrepancy between these two studies suggests that once the first layer of bacterial biofilm has established on the stent surface, it would be more difficult to eradicate (27). Apart from the cost and patient compliance, the use of long-term antibiotic therapy has always raised the concern of cultivating resistant bacterial strains as well as producing untoward effects by altering the bowel flora. Coating the plastic surface with a biocide could theoretically avoid these problems. Silver-coated polyurethane has been tested in vitro and shown to reduce bacterial adherence by 10 to 100-fold (28). The antiadhesion property of silver seems to be a dose-related phenomenon. The possible effect of...