Advances in Gastrointestinal Surgery

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Stomach

Carcinoma Stomach: Current Guidelines for Diagnosis, Investigations and Treatment

Carcinoma of the stomach is a global disease with the highest incidence in Asia, South America and Eastern Europe. The disease is least common in USA and Western Europe [1]. The disease is common among smokers. Other risk factors are *H. pylori* infection, atrophic gastritis, Menetrier's disease and previous gastrectomy. The disease can be genetic as in familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, Peutz-Jegher's syndrome, etc. [2]. Screening for gastric carcinoma is done in high incidence areas such as Japan, Korea and China.

Clinical Diagnosis

The common presenting symptoms of gastric carcinoma are weight loss, anorexia, distaste for protein rich food, indigestion, nausea and vomiting, feeling of fullness even with a small amount of food and anaemia. Haematemesis and melaena can also be present as can gastric outlet obstruction. Similarly dysphagia can be a presenting symptom. Carcinoma stomach should be suspected if these symptoms are present. The diagnosis is established with upper gastrointestinal (gi) endoscopy and biopsy.

Once the diagnosis is made the disease should be staged. Currently CECT of chest, abdomen and pelvis is done. Positron emission tomography (PET) scan may detect metastatic lesions in the lymph nodes or other distal organ(s). PET may be negative in mucinous tumours. Endoscopic ultrasound (EUS) can accurately assess the T and N status. It can also identify the proximal and distal limits of the lesion. Most patients with carcinoma stomach (except those with stage IA) should have

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laparoscopy done. If a positive lesion is detected it should be biopsied. If no lesion is seen, peritoneal cytology is recommended to exclude occult metastatic disease [3]. A comprehensive TNM classification should then be done as described by the American Joint Committee on Cancer Manual, 7th edition [4].

Treatment

All patients shoud be managed by a team of experts including a surgeon, medical and radiation oncologist, radiologist, gastroenterologist, pathologist and nutritionist.

Treatment of local (regional) disease The cornerstone of management of local or locoregional disease is surgery because it can be curative. The extent of resection is dictated by the stage of the disease. T1a tumours can be managed with endoscopic mucosal resection (EMR), provided the lesion is <2 cm, localized to the mucosa and free of ulceration. Since lymphatic spread almost never occurs in these tumours EMR can be curative [5]. The Japanese have expanded the scope of endoscopic treatment to <3 cm in size and extending into the submucosa (T1b) by doing a submucosal resection. Even in this group lymph node metastasis is low [6]. T1 tumours larger than those mentioned above are treated with gastrectomy with resection of perigastric nodes only (D1 resection). For stages IB to III, patients need radical gastrectomy. If a proximal margin of 5 cm can be obtained then subtotal gastrectomy can be done otherwise a total gastrectomy is recommended. Radical gastrectomy should also include both D1 (perigastric) and D2 (along left gastric, common hepatic, splenic and coeliac trunk) lymph nodes [7]. At least 15 lymph nodes need to be removed for proper staging. In randomized trials, the western literature does not show any survival benefit of D2 gastrectomy over D1 gastrectomy [8]. However, in a 15 year follow-up in one Dutch study, lower recurrence and death rates have been reported [9]. This is associated with a higher mortality and morbidity. A meta-analysis from China did not show any survival benefit of D2 resection [10]. Nonetheless, current practice guidelines indicate D2 gastrectomy as the standard of care.

After surgery, all patients should receive further treatment as outlined below:

Adjuvant chemoradiotherapy A combination of cytotoxic agents and radiation therapy has been tried in the USA with improved 5- and 10-year survival compared with surgery alone [11]. Five cycles of 5-FU/leucovorin are given. Patients are also given simultaneous radiotherapy during the second and third cycle—25 fractions over 5 weeks delivering a total dose of 45 Gy. This is the standard treatment in the USA. However, this is not accepted in the rest of the world. The radiotherapy field, when used postoperatively, should include the remnant stomach, including the anastomosis and lymph node bearing area in the stomach bed.

Adjuvant chemotherapy In a meta-analysis published in *JAMA* in 2010, 5-FU-based chemotherapy has shown benefit in overall survival in comparison to surgery alone [12]. This benefit is seen mostly in the Asian population. Similar results have been reported with the use of S1 with capecitabine and oxaliplatin in different clinical trials [13, 14].

Perioperative chemotherapy This is commonly used in UK and Europe. It is given to patients with resectable stages II and III disease. In a comparative study (MAGIC trial) this approach showed better 5-year survival (36% versus 23% with surgery alone) [15]. The regimen followed is 6 cycles (3 before and 3 after surgery) of epirubicin (day1; D1), cisplatin (D1) and 5-FU given from D1 to D21 in each cycle after a 3-week gap. Other European studies have shown equally good results [16, 17]. In the study by Yehon et al. [16] a 28-day cycle was used with cisplatin on D1, and 5-FU on D1–5 every 28 days. Two or three such cycles were administered before and 3–4 cycles were given postoperatively. Cunningham et al. [17] used oral capecitabine instead of 5-FU. Various workers have used this drug along with epirubicin and cisplatin (ECF regime) with equivalent results.

Treatment of advanced disease (with or without metastasis) These patients are not treated surgically. Instead, palliative chemotherapy is recommended with improved life span. The result of such chemotherapy can at times be so good that surgical excision is done in a few patients. Most often a 2-drug regimen is used with cisplatin and 5-FU. The addition of anthracin to these agents has been reported to have better results (overall survival of 11.2 versus 9.9 months). Use of capecitabine avoids the use of intravenous catheter as it is given orally. In one meta-analysis capecitabine was shown to have better overall survival than 5-FU injection/infusion [18].

Various alternative regimens have also been tried for palliation and include irinotecan and 5-FU [19] or docitaxel, 5-FU and cisplatin [20]. This latter regimen is more effective but at the same time more toxic. Other regimens used are irinotecan and weekly paclitaxel but these offer no superiority [21]. Patients who present with bleeding or gastric outlet obstruction can be effectively palliated with hypofractionated radiotherapy [22].

Targetted Therapy

Abnormalities of both proto-oncogene and tumour suppressor gene have been observed in gastric cancer [23]. This information has been used in the management of these cancers. The commonest genetic abnormality seen in gastric cancer is HER-2 positivity, which occurs in 10%–15% of patients. When such patients are treated with trastuzumab, the overall survival improves significantly [24]. The improvement is seen especially in patients who are HER-2 positive with IHC 2+ or FSH positive or IHC 3+ tumour. Trastuzumab is used in combination with cisplatin and 5-FU. Other molecular markers such as VEGF and EGF have also been studied. However, their inhibitors have not shown improvement in overall survival [25, 26].

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Small Intestine

Recent Developments in Small Bowel Neuroendocrine Tumours (NETS)

Currently NET is the commonest malignancy of the small bowel with an incidence of 0.86 new cases per 100,000 population per year in the USA [1]. These tumours tend to progress slowly, are unresponsive to chemotherapy, and when advanced are incurable. Neuroendocrine cells are spread all over the body and tumours arising from these cells can be from any organ. The clinical behaviour of these tumours is related to the site of origin, tumour grade (G1 or G2), proliferative index (Ki-67) and number of mitoses per high power field. NETs by and large are grouped as a single entity irrespective of the organ from which they arise. However, we do not know if this is correct from a therapeutic point [2].

There has been some progress with recent trials of chemotherapy showing promise. Also genetic analyses of these tumours have been published which may further improve results. In addition, positive testing of tumour related RNA or neoplastic cells have been reported for diagnostic purpose. These are discussed below.

Recent Trials Involving Treatment of Small Bowel NETs

As expected all trials reported so far are difficult to interpret because all NETs are pooled together, giving a heterogeneous group, small in number without defined primary endpoints (PEP) and often a single treatment arm.

One of the agents tested is a somatostatin analogue (SSA) [3]. Rinke et al. did a randomized, double blind, placebo controlled study in unresectable, well differentiated (G1) tumours with a proliferation index Ki-67 <2%. Somatostatin was chosen because it binds to somatostatin receptors thereby inhibiting release of hormones [4]. It also has cytotoxic effects [5]. Rinke et al. [3] included 81 midgut NETs, randomized to long-acting release (LAR) octreotide or placebo. They observed longer progression-free survival with octreotide LAR (14.3 months versus 6 months with placebo). It soon got accepted as a standard therapy for unresectable small bowel NET by the National Comprehensive Cancer Network (NCCN) [6]. Other authors have also reported the antitumour effects of SSAs. Caplin et al. [7] reported its efficacy in non-functioning G1/G2 gastroentero-pancreatic (GEP) NETs in which they compared lanreotide analogue with a placebo. The PEP was progression-free survival (PFS). After 24 months of treatment, PFS was 62% in the treatment arm against 22% in the control arm. In yet another study pasireotide LAR was used in GEP NETs (110 patients of which 84 had small bowel NET). In this study instead of PFS, control of symptoms was the PEP. PFS was the secondary end point. The study was prematurely terminated because PEP was not achieved but it showed a significant difference in PFS (11.8 versus 6.8 months) [8]. Mammalian target of rapamycin (mTOR) inhibitor has also been used in a double blind controlled study where both arms received octreotide LAR [9]. mTOR inhibitor, everolimus in 10 mg daily doses was used and 30 mg intramuscular injection of octreotide LAR was used

once in 28 days. A total of 429 patients with NET from various organs were included of which 224 were small bowel NETs. There was discordance in PFS in the study and hence the results are being re-evaluated.

The other development has been the use of anti-vascular endothelial growth factors (VEGF) [10]. The concept was premised on the high vascularity of small bowel NETs. Bevacizumab (Anti-VEGF) was used along with temozolomide (alkylating agent used in chemotherapy). The PEP was response rate. Unfortunately, none of the 7 patients of small bowel NET showed response in this study but 5 of 29 other NETs responded. Lastly, a report of the use of capecitabine and temozolomide in patients with GEP-NETs has been published. Ten of 14 pancreatic and 1 duodenal NET responded [11]. With similar therapy a 70% response rate has been reported for PNETs [12].

All these results seem quite promising and might lead to improvement in patients with unresectable and advanced NETs particularly of the small bowel.

Implications of Genomic Studies in Small Bowel NETs

Multiple studies have been done on the genomic aspects of these tumours. From the clinical perspective: (i) small bowel NETs are genomically stable tumours with low mutation rates [13]; (ii) various alterations as analysed by somatic copy number analysis (SCNA) are responsible for inactivation of tumour suppressor genes or overexpression of growth promoting genes. Recurrent loss of chromosomes 11 and 18 and gain of chromosomes 4, 5, 19 and 20 are seen in these tumours [14]; (iii) Germ line mutation of CDKNIB can cause MEN-4 characterized by parathyroid adenoma, pituitary adenoma and tumours of other endocrine glands including PNET; (iv) Inactivation of CDKNIB, as seen in these tumours, can be used for therapeutic purposes as cell cycle inhibitory drugs can be expected to be useful in the treatment of small bowel NET through this pathway [15].

Developments in Diagnosis

1. A blood test for tumour related RNA [16] circulating in the body can identify patients of NET. The sensitivity and specificity of the test are 79%–88% and 94%, respectively. Thus, it is superior to chromogranin testing which has a sensitivity of 68% with a specificity of 85%.
2. The presence of tumour cells circulating [17] in NET is also being evaluated. In a recent study, nearly half of NET patients were found to have at least 1 circulating cell. The PFS has been correlated with this and it has been found to be a poor prognostic factor.

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Colon and Rectum

Management of Ulcerative Colitis

Ulcerative colitis when severe can be quite disabling. Fortunately this form of disease occurs in no more than 10% of cases. The majority of cases are either of moderate or mild severity (80%–90%). The disease characteristically presents with relapses and remissions. The goal of treatment in ulcerative colitis is to control symptoms, promote mucosal healing and improve quality of life. The treatment is sequential and tailored to the needs of the patient. The options available are use of aminosalicylates, corticosteroids, immunosuppressants and biological molecules such as tumour necrosis factor (TNF)-alpha antibody such as infliximab.

5-Aminosalicylate (5-ASA, Mesalamine)

This is currently the first drug for mild to moderately severe ulcerative colitis and is given orally. In a Cochrane review of 48 randomized controlled trials 5-ASA has been evaluated against placebo and sulphasalazine. The multimatrix system form of 5-ASA has been shown to be the most effective for clinical remission [1]. The drug should be tried for at least a month. Usually it is given in divided doses (500 mg 6 hourly). Clinical improvement of ulcerative colitis with 5-ASA occurs in a dose dependent manner. For complete endoscopic remission the dose often requires to be 3 g per day. Failure to improve (both clinical and endoscopic) does happen with 5-ASA. There is no relation to the frequency of administration of the drug (once, twice or thrice daily). In moderately severe disease higher doses (4 g/day) have been shown to be more effective. In mild disease a higher dose is not associated with better results [2]. Previously treated (with a variety of drugs including 5-ASA, corticosteroids or rectal mesalamine) moderate disease tends to fare better with higher doses of 5-ASA [3]. Simultaneous oral and rectal 5-ASA used for 4–8 weeks has been shown to lead to better remission rates (64%) than with 8 weeks of immunotherapy and oral mesalamine (43%) [4]. 5-ASA is a safe and well tolerated drug. However, abdominal pain, upper respiratory infection (including pharyngitis), anorexia, flatulence or dizziness can occur [1]. 5-ASA is costlier than

sulphasalazine and hence the latter is recommended for induction treatment. It is changed to 5-ASA only if the patient is intolerant to it. Moreover for maintenance too sulphasalazine should be preferred over 5-ASA because of its superiority [5]. A word of caution while using sulphasalazine—it may affect male fertility [5]. Lastly, for longer remission 5-ASA has to be used in higher doses (2.4 g/day) than 1.2 g daily [6].

Corticosteroids

Patients who do not respond to oral and/or rectal 5-ASA therapy even after 2 weeks should be given oral corticosteroids (e.g. prednisone). Remission usually occurs within 2 weeks at a daily dose of 40–60 mg. Once remission occurs, the steroids should be gradually tapered by 5–10 mg every week until a daily dose of 20 mg is achieved. Thereafter, the dose is further reduced by 2.5–5 mg per week. Once the steroid is totally withdrawn patients should be put on 5-ASA. Steroids cannot be used for maintenance. Occasionally for severe disease intravenous injections may have to be used (either methylprednisolone 60 mg daily or hydrocortisone 300 mg daily). The drug can be used as an enema as well which is particularly effective for rectal or left-sided disease. With 1 month of corticosteroid treatment 54% achieve complete response, 30% partial response and 16% do not respond [7]. Intravenous corticosteroid achieves 45%–80% response at 15 days of treatment [8]. Steroid therapy is associated with side-effects including diabetes, hypertension, acne, fluid retention (Cushingoid features), adrenal suppression, infection and osteopenia. In view of these, budesonide (a water soluble analogue of hydrocortisone) with efficacy equivalent to hydrocortisone has been used. It acts locally in colon and whatever is absorbed is detoxicated in the liver.

Immunomodulators

Among the immunosuppressive agents used in ulcerative colitis is azathioprine. The indications are: severe exacerbation of the disease with requirement of oral corticosteroids in a year's time. It is also recommended in patients with moderately severe ulcerative colitis who do not respond to oral steroid therapy. Azathioprine has been shown to have a corticosteroid sparing effect [9]. The dose is 1.5–2.5 mg/kg body weight per day and it is given for 6 months. During this period corticosteroids are either reduced or discontinued. With this schedule the disease usually does not relapse [10]. The drug can be used for maintenance with or without 5-ASA with a similar 2 year relapse rate (19% versus 18%) [11]. A sustained 3 year remission has also been reported particularly when the drug was introduced early (within 3 years of onset of the disease) [12]. The efficacy of the drug for maintenance has been confirmed in a recent Cochrane review [13] but it has to be given for at least one year. Unfortunately, it does have toxicity, notably bone marrow suppression (4%) and acute pancreatitis (2%) [13]. In addition, the incidence of lymphoma on prolonged use of azathioprine is nearly 4 times that in the normal population [14]. The use of thiopurine, which is also recommended for steroid dependent ulcerative colitis, also leads to a similar high risk that decreases with cessation of its use.

Cyclosporine

It is recommended for severe acute ulcerative colitis refractory to corticosteroid therapy. It is given in doses of 4 mg/kg/day intravenously for 14 days. However, it is generally believed that cyclosporine has a short-term benefit and is used before a decision is made to either proceed with surgery or other immunomodulation [15]. Toxicity of cyclosporine includes hypertension, paraesthesias and vomiting.

Anti Tumour Necrosis Factor (TNF)-Alpha Antibodies

These drugs are used for moderate to severe ulcerative colitis. They were introduced in order to avoid steroids in patients not responding to medical treatment or those who had a contraindication to their use. The commonest drug used is infliximab, given as an intravenous infusion in doses of 5 mg/kg over 2 hours. This is followed by an infusion in the second and sixth week. If the response is good patients can be given a maintenance infusion every 8 weeks [16]. A Cochrane review has shown that infliximab can be effective in achieving both clinical and endoscopic response at 8 weeks in patients with moderate to severe ulcerative colitis who are refractory to conventional drugs including steroids and azathioprine [17]. Infliximab can be associated with infections requiring antibiotics, development of antibodies to it, re-activation of tuberculosis and fatal histoplasmosis of the lung. Patients younger than 35 years of age also have a risk of hepatosplenic T cell lymphoma generally when infliximab is used with 6-mercaptopurine [18].

Adalimumab

This fully humanized anti-TNF antibody has been used both for induction and maintenance in patients who do not respond to steroids, immunomodulators or infliximab. Sandborn et al. [19] have reported an effective role of adalimumab. It is usually given subcutaneously, 160 mg (better in 4 divided doses) for 2 days. The drug is repeated at 2 weeks with half the above dose (i.e. 80 mg). It is repeated after another 2 weeks in a dose of 40 mg every alternate week. If there is a response the drug can be continued. Other drugs such as 5-ASA, steroids, azathioprine or 6-mercaptopurine may be continued while adalimumab is given [20]. The same authors have shown significant efficacy of adalimumab lasting for 52 weeks with no serious therapy related effects. It has been suggested that patients who have an early response are likely to have a lasting response beyond 1 year [21].

Golimumab

This is also a fully humanized monoclonal antibody against TNF-alpha. It is also used both for induction and maintenance for clinical and endoscopic response for patients who are non-responsive to other treatments in moderate to severe cases of ulcerative colitis. It is also given subcutaneously at a dose of 200 mg initially followed one week later with 100 mg. Thereafter 100 mg is repeated every 4 weeks. Sandborn et al. [22] have shown that when it is used in moderate to severe ulcerative colitis not responding to 5-ASA, steroids, azathioprine or 6-mercaptopurine, it can induce clinical response and mucosal healing. Remission remained sustained thereby improving quality of life.

To summarise, medical treatment is initiated according to patients' need and is individualized and delivered in a step-wise manner. In mild to moderately severe disease, initially 5-ASA is given. If there is no response steroid therapy is recommended. If steroid therapy is effective then immunomodulators should be started with gradual withdrawal of steroids. If these measures fail TNF-alpha antibodies should be used.

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Faecal Microbiota Transplantation (FMT)

Human faeces have been used for the treatment of diseases by the Chinese nearly 1700 years ago. Even camel faeces have been used for the management of infective diarrhoea during World War II [1]. Eiseman et al. [2] in 1958 used donor faeces as an enema to successfully treat a number of patients with antibiotic-related diarrhoea. Thus faecal transplantation is not really new. It is being increasingly

discussed among physicians because of the increasing incidence of drug-induced diarrhoea including recurrent episodes of infection with *Clostridium difficile* and because of the importance of the gut microbe in various diseases including infective diarrhoea. Unfortunately among both patients and their caregivers—the progress is limited. I discuss this form of treatment, its rationale, method of collection of faeces and its instillation in a recipient, and the results of the treatment.

Normal Colonic Microbial Flora

The various organisms of the colon are Bacteroids, Firmicutes, Actino bacteria and Proteo bacteria. All these bacteria are present in a state of equilibrium all through life [3]. Even though these bacteria are constantly facing various antigens, food, toxic agents and harmful bacteria—the equilibrium is maintained. It is essentially due to colonization resistance, which is a process to establish a balance between protective reactions against a pathogen and tolerance against these organisms. Colonization resistance can be altered with antibiotic use, as a result pathological bacteria get an upper hand and damage the intestinal mucosa causing diarrhoea [4]. The frequency with which such problems are emerging is increasing resulting in an interest in FMT. Moreover, as we started understanding human faecal microbiota more, a pathological relationship between these and certain systemic diseases such as diabetes, obesity, autoimmune diseases, etc. is emerging which are being treated with faecal transplantation. The distinct advantage of FMT is that it can provide the full array of normal gut organisms from a healthy donor unlike treatment by manipulation of colonic bacteria with pre and probiotics. Its efficacy has been shown in an experimental study by Lawley et al. [5]. They induced *Clostridium difficile* infection in mice treated with clindamycin. When the disease was established (ongoing infection, lasting dysbiosis and reduced gastrointestinal microbial diversity [GIMb])—faecal microbiota collected from the faeces of healthy mice was infused into the colon. With this, *Clostridium difficile* infection was arrested and the animal became healthy. It is apparent from the study that antibiotic use (or abuse) causes damage to GIMb. This allows invasion by pathogenic organisms (e.g. *C. difficile*) due to reduced colonization resistance. Once normal microbiota is restored (as with faecal transplantation) GIMb recovers and so does colonization resistance.

Use of FMT in Clinical Practice

The donor is usually a relative and less commonly volunteers.

Screening of Donors

1. Free from sexually transmitted diseases
2. No HIV or hepatitis, cytomegalovirus, syphilis or Epstein–Barr virus
3. No history of travel, sex habits, past operation, blood transfusion, etc.
4. Stool test for *E. histolytica*, parasites, test for *Clostridium difficile*
5. A day before donation current stool frequency and pattern, general health, and any use of antibiotics in particular.

Preparation of Faeces

- Fresh faecal sample 200–300 g is collected, processed and infused as fast as possible.
- Dissolve in sterile saline
- Strain it to remove debris
- Cover the sample as soon as possible
- Samples can be frozen. The advantage being it can be used at any time.

Routes of Infusion

Both upper and lower gastrointestinal (g.i.) route has been used. In the former the infusion is given into the stomach or duodenum through a nasogastric tube. For colonic infusion, colonoscopic installation of the prepared faeces is done. The upper g.i. route infusion is relatively easy but vomiting can be a problem. Colonoscopy on the other hand is more invasive with the attendant risk of perforation and bleeding. In spite of this, this is the route most commonly used.

Preparation for FMT in Recipients

- Bowel preparation may be necessary in some but not in all.
- No antibiotic should be used except in *C. difficile*

Results of FMT in Various Conditions

Clostridium difficile infection This organism is present in the large bowel of nearly 15% of asymptomatic patients and is also present in the environment. It has a potential pathogenic effect. In the normal colon it cannot differentiate and produce its characteristic toxin. However, if the colonization resistance decreases due to any cause (antibiotics, operation, chemotherapy, etc.), it provides an opportunity for these organisms to produce epithelial damage leading to diarrhoea. Once clostridial colitis is diagnosed, metronidazole and vancomycin are used with success. However, nearly one-quarter of patients develop recurrent disease. The management of this group is difficult and hence FMT has been advised. Success has been reported in 94% of patients [6] and is far superior to the results of probiotic therapy. This proves that healthy donor faeces contain a higher combination of colonic bacterial strains. In addition, probably the presence of bile acids, various proteins and bacteriophages in donor faeces make FMT more effective. There is only one randomized study on FMT versus standard vancomycin therapy. The result of FMT was so overwhelmingly superior that the study was prematurely terminated. In the study group in this series *Clostridium difficile* infection resolved in 94% of patients versus 23%–31% in the vancomycin treatment group [7].

Metabolic syndrome In obese mice there is scarce microbial spectrum especially in those who are fed excess fat and carbohydrate. When such fat mice are treated with microbes from leaner ones their total body fat decreases to –30% as opposed to +5% when microbes from obese mice were used [8]. In a human trial, patients of metabolic syndrome when treated with allogenic faeces from a lean donor, reduction of

insulin resistance was noted as compared to those treated with autologous faeces. This highlights the beneficial effects of FMT procured from a lean donor. Both blood glucose and lipid profiles were reduced in the allogenic group [9]. How does this happen? It is surmised that these bacterial supplements produce short chain fatty acids which restore normal physiology.

Ulcerative colitis A number of case series have been published in recent years suggesting the usefulness of FMT in the treatment of ulcerative colitis. This form of treatment was started in 1988 when Bennet and Brinkman [10] used FMT enema for ulcerative colitis. Three months later, no active inflammation of the colon was seen and the patient remained asymptomatic. Borody et al. have reported that this form of treatment gives complete clinical, endoscopic and pathological evidence of remission [11]. Recently a review of the use of FMT for the treatment of ulcerative colitis [12] reported 91.9% overall response with 67.7% complete response. Over 50% of patients undergoing repeat colonoscopy at a mean follow up of 33 months, did not show any mucosal lesion; neither was there any histopathological evidence of disease. Unlike in other diseases, in ulcerative colitis FMT needs to be repeated. The schedule followed is—initially FMT is done colonoscopically, followed by daily enemas for two weeks, this is followed by every alternate day and then twice a week and lastly once a week. The duration of treatment is decided by the clinical response and repeat colonoscopy at 12 weeks. Many patients may need FMT for weeks. It is exceptional for patients to experience cure with one or two FMT enemas. It is suitable even for children with ulcerative colitis [13]. FMT has been shown to be effective not only in ulcerative colitis but also for the associated primary sclerosing cholangitis.

Crohn's disease Though FMT has been studied in Crohn's disease, its effect remains speculative. However, prolonged therapy has been suggested with better expected results [14].

Irritable bowel syndrome (IBS) Both diarrhoea and constipation variants of IBS have been treated with FMT. In a study of 13 patients with IBD (9 with diarrhoea, 3 with constipation and 1 having constipation alternating with diarrhoea), Pinn et al. [15] reported efficacy of FMT. Improvement in abdominal pain occurred in 72%, bowel habits in 69%, dyspepsia in 67%, bloating in 50% and passage of flatus in 42%.

Borody et al. [11] were the first to report that IBS can be cured with FMT. Following their case report, they published a case series of 45 patients with IBS treated with FMT. The first FMT was colonoscopic, while the subsequent ones were delivered by enema. With this 89% of patients got relief from constipation, bloating and abdominal pain almost immediately. On a 9–19 month follow up, 60% of patients were reported to have normal bowel evacuation without the use of aperients.

Autoimmune diseases The benefit of FMT in autoimmune diseases came more as a surprise than by design. In one patient with chronic ulcerative colitis who also had idiopathic thrombocytopenic purpura the platelet count normalized following

successful FMT for his ulcerative colitis [16]. In another report, 3 patients of multiple sclerosis who were treated with FMT for constipation had dramatic improvement of neurological symptoms so much so that they started walking without support (they were on a wheelchair before treatment). Two of these patients, who were on a bladder catheter, had a catheter-free life after FMT. In one patient, 15 years after FMT, no active disease was found on an MRI [17].

Future applications of FMT are envisaged in the treatment of halitosis, autism, nephrolithiasis, acne and Parikinsonism [14]. With human gut microbiota at the centre of research, it is expected that this may establish the relationship of the gut microbiome with various ill understood diseases. As and when that happens FMT will receive a further boost.

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Liver

Hepatopulmonary Syndrome (HPS)

This is a relatively common complication of chronic liver disease with or without associated portal hypertension occurring in 30% of cirrhotics [1]. Patients affected are usually hypoxic as a result of vasodilatation of the pulmonary vascular bed. HPS has a high mortality. The condition is diagnosed in the presence of the following in a patient with chronic liver disease (cirrhosis) and/or portal hypertension.

1. Impaired oxygenation ($PaO_2 < 70$ mmHg and/or Pa–aO_2 (alveolar–arterial oxygen gradient) ≥ 15 mmHg.
2. Positive contrast enhanced echocardiography (presence of bubbles in left heart suggesting right to left shunt; presence of these bubbles after 3–6 cardiac cycles confirms intrapulmonary vascular dilatation (IPVD).
3. Perfusion lung scan (done with radioactive technetium labeled macroaggregated albumin) usually shows trapped albumin in the pulmonary vasculature. In HPS, because of IPVD, the albumin particles pass through the pulmonary microcirculation to the brain.

Causes

1. Cirrhosis of any cause.
2. Acute and chronic hepatitis without cirrhosis [2]
3. Non-cirrhotic portal hypertension without chronic liver disease [3]

Pathophysiology

The central event in HPS is dilatation of the intrapulmonary vasculature. As a result of this, mixed venous blood is rapidly shunted into the pulmonary vein and gross ventilation–perfusion mismatch occurs resulting in hypoxaemia. This defective gas exchange worsens in decompensated cirrhosis wherein alveolar–capillary diffusion impairment occurs leading to a decrease in total oxygenation of the blood. The vasodilatation occurs because of nitric oxide (NO) production both by eNOS (endothelial nitric oxide synthase) from pulmonary vascular endothelial cells and by iNOS (inducible nitric oxide synthase) of macrophages [4].

Some newer insights into the mechanism of pulmonary vascular bed dilatation come from the common bile duct ligation (CBDL) model in experimental animals. Such animals have proliferating cholangiocytes in the liver that produce and secrete endothelin 1 (ET-1). After CBDL, the animal develops cirrhosis and a hyperdynamic circulation. This leads to increased stress in the pulmonary vascular bed. There is expression of endothelin B receptors in the pulmonary vasculature. The increased plasma levels of ET-1 and over expression of endothelin B receptors stimulates production of nitric oxide via eNOS [5].

There have been studies on alternate pathways for this phenomenon including the role of monocytes, TNF-alpha and angiogenesis. Monocytes have been shown to increase in the pulmonary vascular system in CBDL rats. These cells increase NO level (through stimulation of iNOS) and CO (through heme oxygenase-1) resulting in vasodilatation. Endothelins seem to have a role in this because they help monocyte adherence in the pulmonary vascular bed by production of monocyte chemokine, fractalkine (FKN) which causes angiogenesis both directly and through VEGF production by monocyte related action [6]. The anti-VEGF action of sorafenib (a tyrosine kinase inhibitor) reduces monocyte adhesion in the pulmonary vascular bed and has been shown to improve oxygenation in the CBDL model [7]. It is being keenly watched if this can occur in human HPS also.

The role of Annexin A1 and A2 has also been studied in the pathophysiology of HPS. While annexin A1 level is decreased following proliferation of pulmonary microvascular endothelial cell (PMVEC), annexin A2 is increased for pulmonary artery smooth muscle cell (PASMC) proliferation. Over expression of annexin A1 and inhibition of annexin A2 improves oxygenation in the CBDL model [8, 9]. Translocation of bacteria and endotoxaemia has also been hypothesized to be involved in HPS. A glucose-regulated 78 KDa protein, a marker of TNF-alpha and endotoxin has been shown to be increased in the lungs. This protein decreased following treatment with levofloxacin. This is presumably due to the control of bacteraemia and inflammation [10].

Improvement in hypoxaemia by TNF-alpha monoclonal antibody has established the role of TNF in the pathogenesis of HPS [11].

Developments in the Management of HPS

1. *Pentoxifylline*: In the past this drug has shown variable results. However, a recent study has shown an increase in PaO_2 of 26 mmHg with the use of pentoxyphylline [12].

2. *Mycophenolate mofetil*: Recently a case has been reported in which the drug has been shown to achieve resolution of HPS in a boy with non-cirrhotic portal hypertension [13]. This is possibly due to the anti-angiogenetic effect of the drug. It is also possible that inhibition of ET-1 and NO production is responsible for improvement in oxygenation with the use of mycophenolate.
3. *TIPS*: Notwithstanding the above results treatment of HPS continues to be poor. Interest to lower the portal pressure to treat HPS has thus been pursued. Two case reports published in the past 2 years have shown that TIPS improved oxygenation [14, 15]. The only problem is the results of TIPS are not consistent. However, since TIPS does not worsen the oxygenation it can be used for HPS in patients with refractory ascites and variceal bleeding.
4. *Liver transplantation*: This is the only viable option to satisfactorily improve oxygenation in patients with HPS. The problem is the availability of a cadaveric donor. Since these patients have good liver function they are unlikely to get a liver too soon. Patients with PaO_2<60 mmHg (who are otherwise candidates for liver transplantation) can be offered MELD exception so as to get an organ. It has been reported that, with such an exception, patients live longer in the pre-transplant period than those without HPS. Moreover, post-transplant survival too in the MELD exception group is similar to those without HPS [16, 17].

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Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease. The disease is characterized by destruction of the small and medium sized bile ducts of the liver. As a result patients develop features of cholestasis leading to cirrhosis. The disease is seen predominantly in middle-aged women, often associated with other autoimmune diseases such as Sjogren's syndrome, systemic lupus erythematosus, etc. The presenting features include fatigue, pruritis and at times features of portal hypertension. Many patients remain asymptomatic. The latter patients are diagnosed by an elevated alkaline phosphatase (ALP) and raised antimitochondrial antibody (AMA) titres. Liver biopsy, when done, shows cholangiopathy. Patients can also present with sequelae of chronic cholestasis such as osteoporosis and coagulopathy (due to vitamin K deficiency).

Incidence

The incidence of PBC has been reported to be around 40 per 100,000 population [1–3]. Thus it does not seem to be as uncommon as had been thought in the past. As mentioned earlier, the disease is more common in middle aged women. It is well known that oestrogen is involved in the maturation of lymphocytes with resultant synthesis of antibodies and cytokine [4, 5]. The fact that PBC does not occur before puberty substantiates the view that there is a possible role of oestrogen in the disease process. Gender seems to have a bearing on the prognosis of PBC. Men tend to have less pruritus than women but a higher incidence of hepatocellular carcinoma [6, 7].

Pathogenesis

The pathogenesis of PBC is related to both genetic and environmental factors. Genome wide association studies (GWAS) in the USA [8] have linked PBC to HLA class II and interleukin (IL-12). UK and Italian studies [9, 10] have identified 12 and 3 more loci in addition to IL-12A and IL-12RB2 identified in the American study. The Japanese GWAS has shown ethnic differences [11]. All these studies have established the relationship of 27 non-HLA PBC risk loci. These have suggested the role of nuclear factor kappa-beta (NFKB), T cell differentiation, toll-like receptor and tumour necrosis factor (TNF) in the pathogenesis of PBC. Thus, there is gross genetic heterogeneity in PBC across geographic and ethnic populations. To move forward, GWAS have opened the area of genetic treatment of PBC by adopting measures directed against IL-12/23. The environmental factors implicated in the pathogenesis of PBC include chemicals, bacteria and substances foreign to the body (xenobiotics). All these can cause alteration of native mitochondrial protein of the host AMA. This process can initiate an immune response in the host and the original protein becomes an autoantigen [12]. This is considered a key factor in the pathogenesis of PBC.

Clinical Features

Most patients are asymptomatic (more than 60%) at presentation. Nearly half of them develop symptoms within 10 years. These include fatigue, pruritus, dryness of the mouth or eyes. Jaundice, hepatosplenomegaly, xanthelasma and cutaneous pigmentation are rarely seen. Fatigue is a disturbing symptom with a poor quality of life. In a prospective study reduced survival was seen in patients of PBC with fatigue [13]. Liver transplantation can improve fatigue but after 2 years the fatigue returns [14]. Pruritus in PBC is caused by stimulation of itch-related nerve endings by pruritogens such as histamine, serotonin and gastrin releasing peptide receptors [15]. Previously cutaneous bile acids were thought to be responsible for pruritus because bile acid binding agents led to improvement. However, there is no direct relation between skin or serum bile acids and pruritus. It is possible bile acids may act through stimulation of other itch neurotransmitters such as autotoxin [16].

Complications

1. Keratoconjunctivitis sicca, but not Sjogren's.
2. Hyperlipidaemia in early disease, decreasing drastically once end-stage liver disease develops.

3. Fat soluble vitamin deficiency can occur when cirrhosis develops.
4. Osteoporosis is quite common in PBC. Advanced age, disease activity and female sex are contributing factors. In advanced cases osteoporosis can be crippling with 21% fracture rate [17].
5. Hepatocellular carcinoma can also develop, particularly in men.

Investigations

Characteristically the ALP is raised (more than 1.5 times of the upper limit). The ALT and AST can be moderately increased while the serum bilirubin remains normal.

Serology AMA is raised in PBC in 95% of patients. The antinuclear antibody (ANA) and smooth muscle antibody (SMA) can be raised in over 50% of patients. Autoantibodies such as rheumatoid factor and antithyroid antibodies can also be raised in some patients.

Histology The characteristic histological features of PBC are: (i) portal tract inflammation; (ii) lymphoplamacytic infiltration of the bile ducts; and (iii) obliteration of the bile duct with a granuloma is considered pathognomonic.

These features are present in stage I PBC. When the disease progresses, additional features such as lymphocytic cholangitis and interface hepatitis can be seen (stage II PBC). Bridging fibrosis is present in stage III PBC. Stage IV PBC is characterized by frank cirrhosis [18].

Variants of PBC

All the above characteristics may not be present in all patients. Sometimes AMA may not be positive. At times AMA positive patients have features of autoimmune hepatitis (AIH) in addition to non-pyogenic cholangitis. Thus patients may be categorized as:

1. AMA negative PBC, and
2. PBC with overlapping AIH

However, patients with AMA negative PBC may have ANA and SMA in their blood. A liver biopsy, though invasive, will help make the diagnosis in these patients. Recently, an enzyme linked immunosorbent assay has been developed which uses 3 different antigens. Nearly all (90%) PBC patients who are AMA negative by conventional methods [19] can be diagnosed with this. AMA negative PBC has less pruritus, lower ALP and higher incidence of other autoimmune diseases. AMA negative PBC does better with ursodeoxyxcholic acid (UDCA) and immunosuppressive treatment [20].

It is often difficult to differentiate bewtween PBC and AIH. The two can co-exist in the same patient. In still other variants, patients on treatment for PBC may develop AIH. Both these entities are called ‘overlap syndrome’. At the moment this is defined on the basis of features of both.

1. AIH: Interface hepatitis, raised IgG/anti-SMA, ALT (5×)
2. PBC: AMA+, raised ALP and positive histology

These patients are managed with UDCA or a combination of UDCA and steroid/azathioprine. A study has shown the efficacy of steroids when UDCA does not help. The effects were confirmed on histology and biochemistry [21]. Those who do not respond are treated with immunosuppressants (such as azathioprine) as well as UDCA with improvement in 73% of patients. Some patients fail to respond to initial immunosuppressive agents but respond to second line drugs such as cyclosporine, tacrolimus or mycophenolate mofetil [22].

Treatment

Various drugs have been used including D-penicillamine, steroids, azathioprine and colchicines but these are not very effective.

UDCA is the drug of choice for the management of PBC. Both randomized trials and observational studies have shown its efficacy. The recommended dose is 13–15 mg/kg/day for early stage PBC [23]. However, response is seen in only 50% of patients. It must be ensured that compliance is good, the dose is adequate and simultaneous use of cholestyramine is avoided. One has to rule out existing autoimmune thyroiditis, coeliac disease or overlap syndrome before declaring the patient treatment failure. Response can be identified with reduction of ALP and AST/ALT falling to less than 1.5-times the normal [18]. Combination therapy with UDCA and azathioprine, steroids and immunosuppressants has also been tried but the efficacy is not as good as was anticipated. Recently, budesonide has been used. The rationale for its use is that 90% of the drug is absorbed from the small bowel and gets metabolized in the liver in the first pass itself. A prospective double blind study has shown its efficacy [24]. Both liver enzymes and IgG and IgM decreased and there was improvement in liver histology (inflammation and fibrosis).

Fibrates (bezafibrate and fenofibrate) are new drugs used in clinical practice in Japan and USA [25]. These have been claimed to increase the phospholipid output in bile and decrease the damaging effects of bile on the cells. With their use reduction in liver enzymes has been achieved. The drug can be used singly or in combination with UDCA.

The other new drug is 6a-ethyl-chenodeoxycholic acid (obeticholic acid). It is a natural ligand for farnesoid x receptor (FxR) which controls bile production. Obeticholic acid is 100 times more potent than FxR agonist. Once stimulated (FxR) by obeticholic acid, bile production decreases and the flow of bile increases. As a result, stasis of toxic bile acid is prevented. It also has an antifibrotic effect [26]. Lastly, liver transplantation can be done though it is reserved for end-stage liver disease due to PBC. However, intractable pruritus even in early stages of PBC is an indication for liver transplantation. Patient and graft survival of 90%–95% at 1 year and 80%–85% at 5 years has been reported [18]. However, recurrence of PBC at 10 years is a problem and occurs in nearly one-third of patients. The identified risk factors are older donor and use of tacrolimus.

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Biliary Tract

Current Status of Surgical Treatment for Gall Bladder Cancer

Before we discuss surgical treatment, let me begin with the anatomical peculiarity of gall bladder that has a bearing on the tumour progression. Also, since surgery is based on accurate stage, staging needs to be discussed.

Anatomical Peculiarities of Gall Bladder

The gall bladder has mucosa, but no submucosa. Mucosa is attached to the lamina propria. Outside this lies the muscle layer (muscularis propria) and the perimuscular connective tissue. The entire gall bladder is enveloped by serosa except the part of the gall bladder attached to the liver. Due to this, perimuscular connective tissue is continuous with intrahepatic connective tissue. This has a bearing on the direct extension of gall bladder cancer into the liver and in fact it is the commonest way of spread of gall bladder cancer. Direct spread via the cystic duct, surprisingly is very rare. When it does occur, it commonly invades the liver; because thickness of the liver tissue lying between the neck of the gall bladder and cystic duct and right hepatic duct is only 1.6 mm. To achieve 2–3 cm of clear margin, one has to do an anatomical liver resection [1].

Staging of Gall Bladder Cancer

The TNM staging system of the Americal Joint Committee on Cancer is widely followed as given below [2]:

Primary tumour (T):	Tx – Primary tumour can not be assessed	
	T0 – No evidence of primary tumour	
	Tis – Carcinoma *in situ*	
	T1a – Tumour invades lamina propria	
	T1b – Tumour invades muscular layer	
	T2 – Tumour invades perimuscular connective tissue, no extension beyond serosa or into liver	
	T3 – Tumour invades serosa and directly invades liver and/or one organ or structure.	
	T4 – Tumour invades main portal vein or hepatic artery or invades at least two extrahepatic structures or organs.	
Regional lymph nodes (N)	Nx – Regional nodes can not be assessed	
	N0 – No node, metastasis	
	N1 – Nodes along cystic duct, CBD, hepatic artery and/or portal vein	
	N2 – Metastasis to periaortic, superiormesenteric &/or celiac artery nodes.	
Distant metastasis:	M0	No distant metastasis
	Ml	Distant metastasis
Staging:	Stage 0	Tis N0 M0
	Stage I	T1 N0 M0
	Stage II	T2 N0 M0
	Stage IIIA	T3 N0 M0
	Stage IIIB	T-T3 N1 M0
	Stage IVA	TA N0–1 M0
	Stage IVB	Amy T, N2 M0 or Amy T, Amy N and M1

Stage I is localised disease and is seen in only a minority of patients. These tumours can be removed completely surgically. For T1a tumours the 5-year survival following complete removal is 100%. On the other hand T1b tumours have poor survival (15% at 5 years).

Unresectable disease is present in the vast majority of patients. Complete removal is not possible in this group essentially due to extensive liver infiltration, lymphatic metastasis or dissemination intraperitoneally. Distant metastasis, though can occur, is uncommon. This group of patients can only be given palliative therapy.

Surgical Treatment for Gall Bladder Cancer

Early disease Lee et al. [3] through an extensive search of 2312 publications (29 of which met eligibility criteria) have shown that most authors favoured simple cholecystectomy for T1a and T1b disease. Five year survival in T1a patients was 100%. They also showed lymph node metastases occur in 11% of T1b disease and 2% in T1a disease. In this review, 1% of T1a and 9% of T1b disease patients died of recurrent cancer. Thus simple cholecystectomy has been shown to be adequate for T1a disease. They could not find any survival advantage of extended cholecystectomy for T1b disease. However, both National Cancer Database (NCDB) and SEER support extended cholecystectomy for T1b gall bladder cancer. Further, a multicentre study has evaluated 115 cases of re-resection (after initial cholecystectomy) for gall bladder cancer. Residual disease was reported in 46% of cases. On the basis of this, the authors advised extended resection for T1b disease [4].

In this connection the SEER database needs some discussion. It has over 3000 patients—12% Tis, 30% T1 and 58% T2. Poor survival noted in this database includes age above 60 years, more advanced cancers and positive lymph nodes. Survival was better in female patients and patients undergoing radical (extended) cholecystectomy. Better survival noted was restricted to patients having T2 disease.

Lymph node dissection It was seen that survival was better when 1–4 lymph nodes were removed versus when no lymph node was removed. Similarly when 5 or more lymph nodes were removed patients lived longer than patients on whom 1–4 lymph nodes were removed. This improved survival following lymphadenectomy was seen in T2 lesions. Based on these observations, extended resection with lymph node dissection seems to improve survival in T2 tumours [5].

Incidental carcinoma of the gall bladder The incidence of such tumours is on the rise in the era of laparoscopic cholecystectomy. Often, the pathology report of the cholecystectomy specimen showing malignancy comes as a surprise. What to do in such situations, in the absence of any guideline, is difficult to decide. Should all such patients be reoperated? In an old but significant study [6] it was observed that reresection (extended cholecystectomy) for T1a did not have any benefit. However, patients with T1b lesions had a significant benefit. In this latter group tumour recurrence was significantly lower than in those with T1b tumours not undergoing reoperation. Hence the decision to reoperate largely depends on the depth of tumour infiltration into the gall bladder wall. Tumours infiltrating into the muscular layer (T1b) should have reoperation and a formal extended cholecystectomy done.

Advanced disease T2 lesions involve the connective tissue beyond the muscular layer. Consequently, it infiltrates the parenchyma of segments IVB and V of liver. It stands to logic therefore that *en bloc* resection of the liver bed along with gall bladder tumour is done for this category of patients. Zhu et al. [4] have shown in a series of 98 patients of gall bladder cancer that nearly half the number are due to T2 disease. Five year survival following simple cholecystectomy and radical cholecystectomy in this series were 40% and 90%, respectively. In view of this, patients of T2 gall bladder cancer who are fit and without evidence of widespread disease should be offered radical cholecystectomy.

Impact of hepatectomy and extrahepatic bile duct excision has been evaluated by Yakomizo et al. in one Japanese study [7]. They have shown 73% 5 year survival following hepatectomy for pathological T2 gall bladder cancer as opposed to 87% for those without hepatectomy. Similarly, excision of extrahepatic bile duct was associated with 67% 5 year survival as against 81% without bile duct excision. Thus, more radical operation does not appear to offer any significant survival benefit. However, it can give the status of resected margins.

Lymph node dissection, on the other hand has a direct relationship with survival (see earlier section of this review).

Given this background, hepatectomy and extrahepatic bile duct excision can be avoided provided surgical margins are negative. Lymph node dissection should be carried out for all advanced operable carcinoma of the gall bladder.

T3 tumours As per definition they involve one additional structure other than liver. Thus they can be surgically removed. But the morbidity can be substantial. With aggressive surgery 20% long term survival can be expected [8].

T4 tumours (Please see definitions in earlier section of this review.) These tumours have an anatomical extension into vital structures (portal vein, hepatic artery with/without other visceral involvement), and most such patients are not candidates for surgical treatment. This is because of serious issues concerning mortality and morbidity. This opinion is reflected in the review of 724 cases of gall bladder cancer by the French Surgical Association in which the overall survival time was shown to be 2–8 months [8].

The gloomy outlook has, however, been somewhat better in recent times. Properly selected patients with advanced imaging techniques including PET scan can undergo multivisceral resection with no undue mortality with some long term survival [9].

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Pancreas

Chronic Pancreatitis

Chronic pancreatits can be extremely disabling in advanced stages. Despite a large number of therapeutic options, most patients never become asymptomatic. There lies the importance of early diagnosis in order to make therapeutic attempts effective. While in full blown chronic pancreatitis the diagnosis is straight forward, in the early stage of the disease this is not always possible. Two investigations that have been useful for this purpose are (i) pancreatic function tests after secretin stimulation and (ii) endoscopic ultrasound evaluation of the parenchymal morphology of the pancreas. Pancreatic function test is the most sensitive test for early diagnosis of chronic pancreatitis [1]. Unfortunately the test is not available in most centres. Following stimulation the duodenal bicarbonate level is measured and based on the results a diagnosis of chronic pancreatitis is made as given below:

<50 mEq/L: Chronic pancreatitis
50–75 mEq/L: Indeterminate
>75 mEq/L: Normal

Ketwaroo et al. [2] have retrospectively evaluated the utility of pancreatic function tests (PFT) for the diagnosis of chronic pancreatitis. Twenty patients with abnormal PFT were followed upto 11 years. These patients did not have abnormalities on imaging. They found chronic pancreatitis developing in 45% of cases (versus

only 3% for those with normal PFT). The test though seems good to exclude chronic pancreatitis, it has substantial false positivity. With the availability of MRI, CT and EUS, this test is losing its appeal.

Before EUS was available, the diagnosis was made on the basis of morphological abnormalities of the duct evaluated by ERCP (Cambridge Grading Sysem) [2] as given below:

Grade	Pancreatic duct	Side branches
Normal	Normal	Normal
Equivocal	Normal	<3 abnormal
Mild	Normal	≥3 abnormal
Moderate	Abnormal	≥3 abnormal
Marked	Abnormal + one or more of the following: (i) Large cavity (>10 mm) (ii) Ductal obstruction (iii) Severe duct dilatation or irregularities (iv) Intraductal filling defect or stone	≥3 abnormal

EUS has the ability to visualize the pancreatic duct as well as the parenchyma. Nine features (as given below) are defined. The presence of at least 3 is necessary for the diagnosis of chronic pancreatitis. The advantage of EUS over ERCP is its ability to identify abnormalities not shown on ERCP in the minor ducts.

EUS criteria (Rosemont criteria) [3]

Ductal findings	Parenchymal findings
1. Dilated main duct	6. Hyperechoic foci
2. Dilated side branches	7. Hyperechoic strands
3. Duct irregularity	8. Gland lobularity
4. Hyperechoic duct margin	9. Cystic cavities
5. Stones/calcification	

EUS has been shown to be more sensitive than CT and MRI for the diagnosis of early chronic pancreatitis. The problem arises when one considers the similar imaging findings of EUS in elderly patients who are alcoholic, smoker, diabetic and nephritic. To improve the results of EUS in these scenarios (as well as to rule out malignancy), contrast enhanced EUS and computer aided image analysis has been developed [4, 5]. More recently EUS elastography has been developed which corroborates with EUS features of chronic pancreatitis [6]. Contrast enhancing low and high mechanical index techniques have recently been added to EUS elastography. This has been shown to differentiate focal pancreatitis from cancer [7]. Improvement in MRI technology has been reported with the use of secretin stimulation MRI. It provides functional status of the pancreas at the same time. With spectroscopy and spin labeling, it gives quantitative assessment of the features of MR [8]. However, these new techniques (both EUS and MRI) have high false positive and negative results.

Nutritional Impairement in Chronic Pancreatitis

Malnutrition in chronic pancreatitis is multifactorial and can be related to exocrine deficiency (maldigestion), fear of pain and alcohol intake resulting in an inadequate diet. Increased metabolic demand (related to severity of disease) too can lead to malnutrition. The measures to improve malnutrition are: cessation of alcohol and smoking, control of pain, modification of the diet (less carbohydrate and protein [1 g/kg] and fat intake equivalent of 30%–40% estimated calories) and supplementation of pancreatic enzymes (40–50,000 units of lipase per meal). Vitamin deficiency of A, D, E, K and B_{12} should be corrected. Supplementation of zinc, magnesium, calcium, thiamine and folic acid is also required, because these deficiencies are quite common in chronic pancreatitis (often in apparently healthy or even obese patients) [9]. Patients of chronic pancreatitis can also have abnormal bone mineral density (BMD) and careful search for fat soluble vitamin deficiency particularly vitamin D should be done. Osteoporosis and osteopenia are common in chronic pancreatitis [10]. A Dutch study has even reported high incidence of bone fracture specially in young patients [11].

Problem of Diabetes in Chronic Pancreatitis

Diabetes is an important issue in chronic pancreatitis. The problem is two fold, first the disease itself (due to destruction of islet cells) causes diabetes and diabetes acts as a risk factor for pancreatic cancer. Diabetes in chronic pancreatitis is especially problematic because it occurs against the background of pancreatitis related malnutrition, exocrine insufficiency and associated maldigestion. Diabetes in chronic pancreatitis is labelled as type 3C diabetes [12]. The diabetes in such situations is quite brittle and patients often go into hypoglycaemia even with small doses of insulin. The diagnosis should be ascertained by estimating both blood sugar and haemoglobin A1c (glycosylated haemoglobin). All such patients should be provided pancreatic enzyme supplements to achieve adequate secretion of incretin (insulin stimulant), proper antidiabetic treatment along with improved nutrition [13].

Genetics of Chronic Pancreatitis

Various genes play a role in chronic pancreatitis. These are protease serine 1 (PRSS1), Cystic fibrosis transmembrane conductance regulator (CFTR), chymotripsin C (CTRC) and serine protease inhibitor kazal type 1 (SPINK-1). Alcohol related chronic pancreatitis is believed to be induced by polymorphism of tight junction protein (Claudin-2) [14]. Similarly early onset chronic pancreatitis has been shown to be related to carboxypeptidase gene (CPA 1) [15]. In tropical pancreatitis the CTRC gene has been implicated [16]. It is to be mentioned here that genetic abnormalities have just been identified and thus genetic testing on a routine basis is still not recommended.

Autoimmune pancreatitis (*AIP*) is increasing in incidence. There are 2 different types of AIP: Type 1 and 2. Type 1 AIP involves multiple organs including pancreas. These organs are salivary glands, kidneys, bile ducts, retroperitoneum, etc. This form of AIP is associated with raised IgG4. Type 2 AIP occurs exclusively in the pancreas. It is not associated with elevated IgG 4. Both types of AIP respond to

steroids failing which immunosuppressive therapy like azathioprine or even rituximab may have to be used. What happens to AIP in the long run is being investigated. It has been opined that both pancreatic stone and malignancy spares the gland [17, 18].

Pain Management in Chronic Pancreatitis

Pain in chronic pancreatitis occurs due to various factors as discussed in another section in this volume. Treatment of pain starts with stopping alcohol and smoking. Pancreatic enzyme supplement and antioxidants are also used. In early stage of the disease, pain may be managed with analgesics but as the severity increases, patients more frequently require opioids. Addiction to opioids is a genuine problem because of severity of pain with resulting depression. Adjuvant treatment with opiod therapy is often used. Pregabalin has been shown to have a modest effect in one randomized study [19]. Tricyclin antidepressants and serotonin inhibitors have also been used [20]. Pain which does not improve with the above may benefit from endoscopic treatment for stone and stricture of the pancreatic duct. Alternatively, surgical management can be undertaken which has shown better and sustained result (i.e. pain relief). Various endoscopic treatments have already been discussed in another section of this volume. Various surgical approaches are lateral pancreatojejunostomy or head coring/excision operations (Frey or Begger or Berne). Both forms of surgical treatment have their supporters with equal results [21, 22]. All patients after surgery should receive pancreatic enzyme replacement therapy. Total pancreatectomy is seldom done in current surgical practice. However, it may have to be considered for patients who fail to respond to both surgical and non-surgical therapies and are troubled with severe pain and complete exocrine and endocrine insufficiencies. It is also done for prophylaxis against development of pancreatic cancer in hereditary or familial pancreatitis [23]. Total pancreatectomy and islet cell transplantation are increasingly being done in selected centres. With this, pain severity is reduced, as is the insulin requirement. In fact, 46% of patients at 5 years and 10% at 8 years following this surgery are free of insulin [24]. It is not clear when surgery should be done. Opinions vary: one group feels it should be done early before opioid dependence develops. To answer the question of timing a Dutch study is in progress which may enlighten us on this issue [25].

For management of bile duct stricture, pseudocyst, etc., please refer to endoscopic treatment of chronic pancreatitis discussed elsewhere in this volume.

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Endoscopic Treatment of Chronic Pancreatitis

Chronic pancreatitis is a complex condition, plagued essentially with pain of variable severity. Pain in chronic pancreatitis can be attributable to parenchymal changes, causing ductal obstruction with or without a stone inside. The resultant increased pressure inside the duct can cause pain. This is the simplest way to explain pain in chronic pancreatitis. However, associated inflammation and neuropathy of pancreatic nerves can also cause pain. When chronic pancreatitis is complicated as with pseudocyst, or biliary and gastric obstruction the pain can be distressing. Concomitant presence of a malignancy in the setting of chronic pancreatitis is yet another cause of pain.

Endoscopic treatment is essentially directed to relieve obstruction of pancreatic, biliary or gastric obstruction. It is also used to manage pancreatic pseudocyst as well as for coeliac ganglion block for refractory pain.

Pancreatic Duct Stone

Applying extracorporeal shock wave lithotripsy (ESWL), pancreatic stones can be fragmented and subsequently cleared with endoscopic cholangiopancreatographic technique (basket, dormia or mere flushing) [1]. Stone fragmentation can be facilitated with intravenous injection of secretin [3]. ESWL is reported to cause 100% stone fragmentation with a stone clearance rate of 75% [4]. Complete pain relief is reported in 55%–91% of patients only [5]. Tandan et al. [6] have reported a large series of ESWL in chronic pancreatitis. Over 75% stone clearance and complete pain relief were noted in this series. 68.7% of patients at 2–5 years and 60.3% at more than 5 years were pain free. Stone recurrence was reported in over 15% of patients for which repeat ESWL was needed in 3.8%. Recurrent pain was related to stone in only 50%. Understandably, at least 50% of patients who had pain are not due to stones. Relief of pain following ESWL and stone clearance has also been reported by Seven et al. [7]. Even quality of life has been shown to improve in this report. This study has also compared results of ESWL with surgery and shown pain free patients are more in ESWL group than the surgery group.

Pancreatic Duct Stricture

Placement of a stent (10 F-polyethylene) and its change in 1 year has been considered the first line of treatment for pancreatic duct stricture which occurs in 15% of chronic pancreatitis [2, 8]. Prior dilatation of the stricture may be needed in some patients before a stent is placed. The procedure is successful in the majority (85%–98%) with immediate pain relief in 65%–95% of patients. Notably, over a follow up of 14–58 months, 32%–68% of patients experienced sustained pain relief [9]. Complete freedom from pain (without relapse) has recently been reported in 57% of patients at 5 years of follow up [10]. In this context, relief of pain 1 year after stent removal is considered long term success [1]. This also raises a question as to when to stop further stenting. Dumonceau et al. [1] have suggested that this decision (of no further stenting) is taken after demonstration of pancreatoduodenal flow of contrast after ductal filling and free access of 6 Fr catheter through the stricture.

Biliary Stricture

Stricture of the bile duct can occur in chronic pancreatitis due to various reasons; namely inflammatory oedema, compression of the bile duct by the inflamed enlarged head of pancreas (often laden with heavy stone burden), stricture or malignancy (must be ruled out before endoscopic treatment). The non-surgical options to treat these strictures are:

1. Single plastic stent
2. Multiple plastic stent
3. Fully covered self-expanding metal stent

The use of a single plastic stent to treat bile duct stricture is simple and has been used traditionally. However, the long-term results are not very good; 25% relieved at 46 months follow up [11]. To improve upon this, multiple plastic stents have been placed for 1 year with planned stent changes every 3 months. Success with this strategy has been 92% in the long-term [12] and this has been recommended by the European Society of Gastrointestinal Endoscopy [1]. Fully covered self-expanding metal stenting has been tried as an alternative to the above, but the success rate is not very high. In addition, both proximal and distal migration, and cholangitis have been frequently observed with this stent. Stent removal is also difficult in this group. Stent blockage due to tissue overgrowth is another problem encountered with its use. For blocked stents, another stent has been placed through the previous one with some success [13].

Pseudocysts

One of the complications of chronic pancreatitis is the occurence of pseudocysts in 20%–40% of cases. Asymptomatic patients can have expectant management, but those with bleeding, gastric or biliary obstruction need to be treated. Endoscopic cyst drainage of such cysts has been reported to be safe and cost-effective (versus surgical treatment) [14].

Technical Advances

Many times, due to various reasons, ERCP fails to drain the biliopancreatic systems. Endoscopic ultrasound guided drainage in such situations has been shown to be effective and feasible in a number of studies. Success rate of 100% has been reported by Shah et al. [15] with a complication rate of 10%. Reduction of pancreatic duct size and long-term pain relief has also been reported [16].

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Diagnosis of Pancreatic Cysts: Current Status

Pancreatic cysts are being detected (often when asymptomatic) more frequently due to widely available imaging tools like ultrasound, computerized tomography (CT) or magnetic resonance imaging (MRI). In fact, pancreatic cysts are diagnosed in 20% of MRI studies [1]. Nearly 3% of these cysts are malignant. In terms of number this figure may not look large but the malignancy rate is 35 times higher than in individuals who do not have a cyst [2]. Nearly 74% of these malignancies are detected at the initial imaging. It is estimated that the real prevalence of malignant cysts in the American population is 33/100,000 [3]. On a follow up study from Korea, 1.3% malignancy has been reported [4]. Clearly, the previous notion that pancreatic cysts are non-malignant is not true. Certain cysts however have a greater propensity for malignancy than others. Mucinous and serous cysts are contrasting

examples. While the former has a higher rate of malignancy the latter has a very low rate. Cysts of the pancreas can be classified into:

- Congenital: retention cyst
- Inflammatory: pseudocyst (75%–90% of all pancreatic cysts)
- Cystic neoplasms (10% of all pancreatic cysts)
  - Serous cystadenoma
  - Mucinous cystadenoma
  - Intraductal papillary mucinous neoplasm (IPMN)
- Solid neoplasm with cystic degeneration
  - Pancreatic ductal adenocarcinoma
  - Pancreatic metastasis
  - Solid pseudopapillary epithelial neoplasm (SPEN)
  - Neuroendocrine tumours
- Miscellaneous
  - Haemangioma
  - Lymphangioma
  - Lymphoepithelial cyst.

Of these, mucinous neoplasms have a high malignant potential including SPEN. Serous cystadenomas very rarely turn malignant.

How to Differentiate These Lesions?

All cystic lesions of the pancreas can be evaluated with CT, MRI and endoscopic ultrasound. Accuracy of CT in the detection of mucinous cyst is 70%–80%, but it can accurately detect various subtypes in fewer cases [5]. Detection of mucinous cyst is more accurate with MRI (79%–82%). MRI has additional benefits in that it can identify septae, nodules and ductal communication without the risk of radiation. Use of gadolinium has not been found useful in one study and has been recommended to be used in select cases where MRI without gadolinium is inconclusive in characterizing the cystic lesions [6]. Utility of EUS in the diagnosis of pancreatic cysts has been evaluated by Khasab et al. [1]. They compared CT, MRI and EUS in 154 patients. Accuracy of EUS was 76% (with or without cytology, CEA and amylase estimation) as compared to 48% for CT and 34% for MRI. But EUS alone has not been found good enough in differenting various neoplastic and non-neoplastic cysts (56% sensitivity, 45% specificity and 51% accuracy) as reported by Brugg et al. [8]. When FNA, fluid biochemistry and cytology were added with EUS, the accuracy increases. Lee et al. have published results of cyst fluid analysis [9]. They showed CEA less than 5 ng/mL in serous cyst adenoma, pseudocyst and neuroendocrine tumour with 54% sensitivity and 94% specificity. CEA higher than 192 ng/mL was seen in mucinous cyst (73% sensitivity and 84% specificity). Amylase level less than 250 units/L ruled out pseudocyst (sensitivity 44% and specificity 98%). Mutation analysis for K-ras was not very sensitive but was highly specific for detection of mucinous malignant lesion. Translational research has identified

several markers that can be used in the diagnosis of pancreatic cysts. One such marker is guanidine nucleotide alpha stimulating binding protein (GNAS). It is expressed in excised specimens of IPMN or in the cyst fluid of IPMN. Of all the genes studied in this tumour, GNAS positivity (mutation) was 79%, K-ras 50%, 3% each of tumour protein þ53 and V-raf murine sarcoma viral oncogene homolog B (BRAF) [10]. Micro RNAs are also used in the diagnosis of cystic lesions of pancreas. In a study evaluating 378 mRNAs, four mRNAs were found useful in differentiating serous cystadenomas from IPMN and mucinous neoplasms from branched duct IPMN with 85%–100% sensitivity and 100% specificity [11]. Better sensitivity has also been observed with proteomic study in the fluid aspirated during EUS. Mucin analysis through proteomics has been reported with accuracy rate of 98% as compared to 78% for CEA estimation and 71% for cytology [12]. Tissue metabolites from pancreatic cysts (excised specimens) – glucose and kynurenine were also identified. These two metabolic products are reported to be low in mucinous than in non-mucinous cysts [13].

Along side these developments in the laboratory, confocal endomicroscopy has also been introduced. During EUS, a mini probe can be advanced inside the cyst when real time images can be taken of the cyst wall. In a blinded study endomicroscopy has been reported to be 100% specific and 59% sensitive for mucinous cysts [14].

From the above discussion it is clear that mucinous cysts are more likely to be malignant and hence surgery has been recommended for them including IPMN. However, branched duct IPMN has a lower risk of malignancy and can be observed. All the tools discussed above are not able to differentiate these cysts (neoplasm) from main duct IPMN and mixed type IPMN [15]. CT and MRI with MRCP have been used for this but studies have shown that these misclassify 29% main duct and 21% branch duct IPMN [16]. Thus the challenge to differentiate these lesion continues to bother the clinicians. Resection for all MCN, IPMN (both main duct and branch duct type with solid component, dilatation of pancreatic duct ≥1 cm, presence of nodule with cytology suspicious or suggestive of cancer) has been recommended by the International Association of Pancreatology guidelines for IPMN and MCN 2012 [15]. According to this guideline ‘high risk’ stigmata of cancer includes:

1. Obstructive jaundice in the presence of a cyst of the head of pancreas.
2. Enhancing solid component in a cyst
3. Diameter of main pancreatic duct ≥10 mm

All such patients should undergo resection. The ‘worrisome’ features according to this guideline are:

1. Cyst ≥ 3 cm
2. Thickened or enhancing cyst wall
3. MPD 5–9 mm
4. Non-enhancing mural nodule
5. Abrupt change of calibre of pancreatic duct with distal atrophy.

If the above features are present EUS should be done for cytology. If cytology is positive again patients should undergo surgery. On the other hand, if the above are negative the decision is surveliance based on the size of the cyst:

1. <1 cm: CT/MRI every 2–3 years
2. 1–2 cm: CT/MRI every 2 years
3. 2–3 cm: EUS every 3–6 months. For very young patients needing very long follow up one can resect
4. >3 cm: Surveillance with EUS alternating with MRI every 3–6 months. For young patients surgery can be considered.

Other additional features suggestive of malignancy in branch duct IPMN have also been published. These include nodule size, men above 65 years of age, CA 19–9 >37 unit per ml and cyst size 3 cm [17].

High risk criteria defined by the international guidelines (discussed earlier) have been found to correlate with post-resection pathology. In one study the positive predictive value of 63% for high grade dysplasia or invasive cancer in MCN and IPMN was achieved. Similarly the criteria for branch duct IPMN (positive radiology findings, history of weight loss, history of cancer) correlated well with the pathological diagnosis [18]. Based on a meta-analysis of pathologically confirmed IPMNs, a study identified cyst size >3 cm as the strongest predictor of malignancy followed by pancreatic duct diameter >6 mm, presence of main duct IPMN and followed lastly by symptoms produced by the tumour [19]. Early diagnosis of cancer in IPMN can be ascertained by EUS and ERCP. EUS has been found useful when used as a tool during surveillance with sensitivity of 100% versus 39%–56% by radiology [20]. In another study, however, ERCP has been found to be 86% sensitive for early diagnosis of cancer versus 16%–29% in CT, MRI and EUS [21].

Pancreatoscopy has, in recent times, been used for such purpose. Characteristic findings described are papillary tumour and fish egg appearance. These features are present in 73% of patients [22]. Pancreatoscopy with saline irrigation and aspiration for cytology has also been done in one study with 100% sensitivity and specificity for cancer [23].

Histological subtypes of IPMN can be gastric (73%), intestinal (23%), pancreatobiliary (2%) and oncocytic (0.6%). Intestinal type more commonly have malignancy than the gastric type. Biological markers have also been studied for differentiation of low and intermediate grade dysplasia from high grade dysplasia and cancer in IPMN. These include miRNAs, monoclonal antibody-Das-1, serum glycoprotein (alpha1-anti-chymotripsin, thrombospondin 1, haptoglobin and CA 19–9) [24].

Predictors of malignancy have not been widely studied. However, older patients with cyst size > 6 cm, associated nodule and cyst wall calcification are reported to have a risk of cancer [25]. Having discussed various developments recently reported, one has to come to the reality on the ground. The issue is – what will happen to the cyst? Both patients and their care givers like to know. The answer is difficult because we still do not know much about the natural history of these cysts. Ascertaining the diagnosis preoperatively is difficult and often not possible. In addition, features of

malignancy are uncertain (often having false positivity and negativity). Given this background it stands to logic to excise all such lesions but that is both impractical and not desired for a fair number of cystic pancreatic lesions. Within this constraint the following may be important for consideration [24].

1. With history of acute pancreatitis all cysts are likely to be pseudocysts (high amylase content on EUS aspiration).
2. Serous cystadenoma rarely turns malignant.
3. SPEN has a high malignancy rate (upto 15%)
4. MCN also has a high malignancy rate (6%–27%).
5. IPMN of main duct has the highest rate of malignancy (40%–70%) irrespective of whether they are symptomatic or not.
6. Branch duct IPMN if asymptomatic hardly ever turn malignant. Symptomatic patients develop cancer (increasing in rate over time).

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Advances in Pancreatic Surgery

In this review the following are discussed:

1. Are patients offered surgery uniformly for management of pancreatic cancer? Bilimoria et al. [1] do not think so. They have reported that 40% of patients with resectable pancreatic cancer are never offered surgery. They considered this a 'national failure' (Heading of the article reads so!). He is not alone, Abraham et al. [2] reported that analysis of the records of 20,312 patients showed 37% were resectable at the time of diagnosis (i.e. 7585 patients). Of these 7585, only 3034 patients (40%) were offered surgery. This is particularly so for black and poor patients.
2. Readmission after surgery for pancreatic cancer is often considered an index of poor quality of care; leading to increased hospital stay, perioperative mortality, readmission mortality, etc. However, readmission can not necessarily be related to either the surgeon or the hospital (high volume centre). In a recent study authors have shown that readmission may be related to patients co-morbidity and not to the above two. Therefore, readmission rate alone should not be a quality measurement tool for the surgeon or the centre [3].
3. Pancreatic cancer surgery has been shown to be safe in elderly patients. However, one must carefully select the right patients for this demanding surgery. Preoperative assessment using various geriatric assessment strategies can identify patients with a high risk of complications. Those identified to have high risk can be properly counseled against high risk surgery like pancreaticoduodenectomy [4].
4. Extended pancreaticoduodenal resections including resection of vascular structures are being increasingly practiced by increasing number of surgeons. How justified is this strategy? To answer this Bhayani et al. [5] analysed results of 9927 patients and showed increased morbidity and mortality. A report from Massachusetts General Hospital similarly showed prolonged hospital stay, high ICU stay and high readmission rates [6]. A randomized trial has also been con-

ducted. The results of this study have shown no survival benefit following extended resections for pancreatic cancer. This is time for us to learn the lessons and practise pancreatic surgery more judiciously [7]. As regards vascular resection to achieve R0 status—the problem is somewhat unclear. Multiple studies have shown more complication rate in this setting [8, 9]. I strongly feel, these can be better managed with neoadjuvant treatment often avoiding the need for a vascular resection. Even if it is to be done—it should be done in a high volume centre by a surgeon who is experienced enough to tackle this issue.

5. Stratification of IPMN into branch duct and main duct types is increasingly felt important from the management standpoint. While the main duct type is more frequently malignant or has a higher malignant potential, the branch duct type has very little malignant potential. Thus while main duct type should always be resected, the branch type can be kept under follow up (see the other chapter on this elsewhere in this volume). The problem is how to differentiate these? Image analysis (CT, MRI) is often inaccurate (incorrect diagnosis in 25%–30% of IPMNs [10]). This leads to improper management. Therefore CT/MRI alone cannot be relied on too heavily; instead other biological markers such as genetic, proteomic and metabolomic characteristics that are being developed should also be used.
6. Like IPMN, neuroendocrine tumours of the pancreas are also increasingly encountered in contemporary surgical practice. Biological behaviour of these tumours is not yet clear. Hashim et al. [11] has addressed this issue in an article in the *Annals of Surgery* 2014. They reported poor results in tumours larger than 1.5 cm located in the head with Ki67 index greater than 20% and lymphovascular invasion. Involvement of lymph nodes has been reported to have a bearing on survival following resection (4.5 years with and 14.6 years without lymph node involvement). This highlights the importance of lymphadenectomy while undertaking resection for pancreatic NETs.
7. Management of chronic pancreatitis in children. When the pancreas is grossly damaged making a patient nearly invalid with pain, diabetes and exocrine deficiencies, total pancreatectomy with pancreatic islet cell autotransplantation can be successfully undertaken as has been shown by Chinnakotla et al. [12]. In a report of 75 children they have shown relief from pain in 90% of children. Simultaneously nearly 50% were made long term insulin independent.
8. Pancreatic fistula is a surgeon's nightmare. It occurs in 10%–25% of cases. Octreotide has been used by various surgeons. Its value has recently been evaluated in a randomized trial. The results did not show any significant decrease in pancreatic output in either group (with or without octreotide). Both groups of patients had similar pancreatic fistula rate [13].

   To drain or not to drain the abdomen after pancreatic anastomosis remains a contentious issue. Reports from single centres have suggested not to drain. To address the issue a randomized study has been recently undertaken: one group receiving no drain and the other group received one or two drains. The trial had to be terminated prematurely because patients without drain had significantly higher postoperative (90 days) mortality. The cause of majority of the deaths was intra-abdominal sepsis presumably due to pancreatic leak [14].

9. Minimally invasive surgery (MIS) for the management of pancreatic cancer is rapidly making progress. That it is feasible and safe has been reported by Tran Cao et al. and Zureikat et al. [15, 16]. Apart from less hospital stay, the complication rate appears to be less with MIS (laparoscopic and robotic) than open procedures. Robotic surgery once adequately learnt can be speedier than open and laparoscopic approaches. However, pseudoaneurysm of the gastroduodenal artery appears to be more in robotic surgery (6%) than in open surgery.

Postoperative recurrence of tumours is a known problem of pancreatic surgery for cancer. This is possibly related to missed occult metastasis. To help surgeons to remove such lesions, tumour specific fluorescent markers (antibody) used with appropriate optical gadgets to identify them have been developed. Hiroshima et al. [17] have reported its utility with the use of a hand held fluorescence imaging system for removal of unsuspected peritoneal nodules in animals.

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Stents for Biliopancreatic Drainage

Relieving a blocked bile duct or pancreatic duct is, for quite sometime, being achieved with stent placement. It is done with the help of an endoscope. More recently endoscopic ultrasound is also being used for the insertion of a stent. Stents are used in the management of both benign and malignant strictures, leak and cholangitis. While biliary stents can be both plastic and metallic, pancreatic stents are exclusively plastic.

Biliary Stents

For palliative purposes, malignant biliary obstructions are relieved with insertion of plastic stents. Commonly a 10 Fr stent is used. Larger stent (11.5 Fr) is difficult to insert, and does not provide longer patency [1]. When the situation demands, instead of a single larger diameter stent, side by side 10 FR plastic stents can be placed. In one such study, this approach has been reported to have a long patency of 221 days [2]. Presumably bile flows not only through the stents but also along the side of the stents (if the lumen gets blocked). This practice can address the issue of a blocked stent which is common in plastic stents for which the only other alternative is placement of a self-expandable metal stent (SEMS). SEMS has a better patency profile

than plastic stents. Unfortunately, these are more expensive. SEMS have problems such as occlusion due to reflux of food particles. To solve this particular problem, partially covered stents have been developed. The other alternative is use of SEMS with distal antireflux valve. In one study this latter type of stent has been shown to have significantly less reflux-related cholangitis [3]. SEMS can be covered or uncovered. Covered stents have been compared with plastic stents and have a better patency rate (roughly 385 days versus 153 days with plastic stents) [4]. Covered SEMS have not shown any significant superiority over uncovered ones. More importantly, covered stents are more costly, more likely to migrate and cause more cholangitis than uncovered SEMS [5]. However, in a randomized trial published in the *Americal Journal of Gastroenterology* in 2013, Kitano et al. from Japan have reported better patency rate with covered stents. Stent dysfunction free survival was also better. Even the re-intervention rate was less in the covered stents than in the uncovered group. Stent migration, acute pancreatitis was similar in the two groups—covered or uncovered [6]. Results quite different from the above have also been published. In one such study, Lee et al. have reported no difference in recurrent stent blockage rate, survival or undesired side-effects with either stent. Uncovered stents were blocked more frequently by tumour ingrowth and covered stents migrated and caused pancreatitis more often than uncovered stents [7].

For palliative management of malignant hilar block, it is still not clear what is the preferred type of stent—plastic or SEMS. The latter is particularly more difficult if re-intervention is needed. Often patients need simultaneous bilateral stent placement—in such a situation bilateral SEMS placement in a Y shape is more physiological than side-by-side stent placement. Benign biliary strictures (or injuries) are commonly managed with plastic stents; largely because of its simplicity, wide availability and less cost. However, to maintain a large diameter of the common bile duct multiple stents need to be used. Plastic stents need frequent change. These factors go against the use of plastic stents for benign biliary diseases and have prompted various workers to use covered SEMS. Placement of one SEMS is enough for long-term use. With its use for stricture of bile duct due to chronic pancreatitis—over 60% of stricture resolution has been noted by some [8]. Strictures due to other causes regressed even more. Strictures due to chronic pancreatitis *per se* regress infrequently with SEMS and side-effects such as cholangitis, pancreatitis, stent migration, cholecystitis and new stricture formation have been reported.

SEMS can be used for post liver transplantation bile duct stricture. The advantage of SEMS in this setting is that the duration of stenting is about 3 months unlike 12 months when plastic stents are used even though both are equally effective [9]. One important fact which needs discussion is that covered SEMS having a bigger diameter may cause damage to the biliary epithelium leading to further stricture formation.

Use of Stents in Pancreatic Disease

It is essentially used in benign diseases of the pancreas. Plastic stents are temporarily placed in the pancreatic duct. Apart from its use in the management of stricture of the pancreatic duct, it is also being increasingly used for the prevention of ERCP induced acute pancreatitis. What is not yet known is the size of the stent to be used—3 Fr or 5 Fr. In one randomized study both were found to be equally effective [10]. Stents are recently being placed under endoscopic ultrasound guidance for

management of postpancreatitis fluid collection. Transgastric or transduodenally either plastic stents or SEMS are placed in the collection and are allowed to drain into the stomach or duodenum. A number of studies have proved its efficacy [9].

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Miscellaneous

Endoscopic Management of G.I. Bleeding: What Is New?

Endoscopy has been in use for quite sometime now for the management of g.i. bleeding. Various techniques have been used with varying success. It involves injection (epinephrine, thrombin, fibrin glue, polidocanol, etc.), mechanical

measures such as band ligation or clip application and application of heat (argon plasma coagulator, heater probe application and electrocoagulation). In recent years, few new agents have been added to the above list. These include haemostatic spray, stent for variceal compression and mechanical device. These are discussed below:

Haemostatic Spray

It is a technique by which haemostatic agents are sprayed onto the surface of the lesion without any direct contact. This is particularly useful in difficult areas which can not be accessed easily by traditional endoscopic techniques. The spray can be applied on large surfaces. More importantly, the effect is immediate. Currently there are 3 haemostatic sprays available in the market. Two of these are derived from plants and the other is devoid of human, animal and even plant material. The sprays are:

1. *Ankaferd blood stopper* is derived from 5 different herbs known for their haemostatic properties in Turkey [1]. The product is available in powder form, aqueous solution and as a pad. These have properties by which erythrocyte concentration increases which then participate in the normal coagulation process. The agent also forms a scaffold of encapsulated protein to facilitate clotting [2]. These agents have been successfully used in the control of epistaxis, dental bleeding, and bleeding during urologic and paediatric surgery [3]. From these observations the method has been extended to endoscopic control of variceal bleeding.
2. *Endoclot haemostatic spray*: This preparation too is from plants. It is available in powder form. It is directly sprayed over the site of bleeding through an endoscope, or else it can be delivered by a powder/gas mixing chamber connected to each of the two elements [4]. The product absorbs water at the site of application allowing concentration of platelet, RBCs, and coagulation proteins which facilitate quickened haemostasis. The method has been tried in the management of raw surface bleeding after endoscopic mucosal resection (EMR). With this, effective haemostasis has been achieved. Encouraged with the success, prophylactic spraying has been suggested after EMR irrespective of the presence of post-procedure bleeding [4].
3. *Haemospray* utilizes the haemostatic agent T-325. This is a synthetic product and has no human, animal or plant ingredients. It acts by absorption of water allowing concentration of various products of coagulation. Clot thus formed then acts as a pressure agent. The product comes in a canister which is handheld. This is connected to a spraying catheter. For better efficacy it should be sprayed at least 1–2 cm away from the site of bleeding. The method has been used by Leblanc et al. [5] in various causes of bleeding (like following ampullary resection and biliary sphincterotomy). It was used as the primary mode of treatment and the result was extremely gratifying with immediate control of bleeding. Even when it was used as second line of treatment it was found effective. It has also been used for control of bleeding from malignancies of the stomach,

oesophagus and pancreas with gratifying results. A multicentre study utilizing haemospray has also been published [6]. In this study 63 patients of non-variceal GI bleeding were included. In these, haemospray was used as a safe primary therapy with 85% successful haemostasis.

Use of Stents for Control of Variceal Bleed

Balloon tamponade has long been in use for variceal bleeding, though it is quite infrequent in the current era. One of the problems of this traditional measure is inability to swallow. This has largely been taken care of with the use of covered self expanding metal stent (causing tamponade of varices) when other methods fail to control bleeding from ruptured varices such as pharmacotherapy or endoscopic therapy. The stent allows the patient to swallow and hence parenteral nutritional support is not necessary.

Moreover, following stent placement patients need not stay in the ward or ICU. The stent can be kept in place for roughly 2 weeks when definitive treatment can be undertaken. Following its first description in 2006 by Hubmann et al. [7]. Zakaria et al. [8] and Fierz et al. [9] have reported its efficacy.

Mechanical devices for endoscopic haemostasis Over the scope clip (OTSC) is one device currently used for the purpose of haemostasis. The device is an improvement over the standard endoscopic clips. The force with which the clips are applied is more than the standard one. Also, the tissue grasped for clipping is more with this device. The slippage rate with this is low. OTSC can be applied in areas where fibrosis is more and where standard clips cannot control bleeding. With its use effective haemostasis has been achieved in nearly 80% with technical success of 100% [10]. In a multicentre study comprising 30 patients of bleeding upper and lower gastrointestinal lesions, 96% success rate of haemostasis has been reported by Monta et al. [11]. Thus OTSC appears to be useful when other methods of haemostasis fail. The device, though, is somewhat expensive.

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Current Status of Surveillance of Premalignant Lesions of the G.I. Tract

Oesophagus, stomach and the colorectum are the organs that have premalignant lesions. These are Barrett's oesophagus, gastric intestinal metaplasia and colorectal polyps. All these lesions are kept under surveillance for detection of cancer at an early stage. Endoscopy is the tool for this purpose. In this review current status of endoscopy in this aspect is discussed under each condition.

Barrett's Oesophagus

The condition occurs due to gastro-oesophageal reflux, occuring in about 10% of patients undergoing upper gastrointestinal endoscopy for symptomatic disease. In this condition, normal squamous epithelium undergoes metaplasia resulting in its replacement with columnar epithelium. Varying degrees of dysplasia subsequently occur (from no dysplasia to low grade dysplasia to high grade dysplasia; being 86%, 10%, 20% in incidence) [1]. Barrett's oesophagus is the forerunner of oesophageal adenocarcinoma which has a very poor prognosis. The risk of cancer is 30 times more than in patients who have no Barrett's [2]. Thus, it was thought that with surveillance the disease can be detected early when results of treatment are likely to be better. But it is debated if surveillance is cost-effective and if it has any survival benefit. With reference to the latter, a relatively recent work has not shown any benefit [3]. In addition, a report from USA revealed that the incidence of cancer in Barrett's oesophagus is

decreasing [4]. This may negate the very idea of surveillance as a tool to diagnose cancer early. In the light of these, risk stratification of Barrett's is logical. Dysplasia has long been regarded as a risk factor of oesophageal adenocarcinoma. Other risk factors identified in recent times are:

1. Presence of intestinal metaplasia has been reported to have 3-fold higher incidence versus no metaplasia [5]. This may be related to excess biological instability [6].
2. Length of Barrett's is also a risk factor. Long segment has 7 × higher risk for cancer [7].
3. Presence of ulcer in Barrett's is another factor for tumour progression [7].
4. Inactivation of þ16 and þ53 (tumour suppressor genes) also has a higher risk of cancer [8].
5. Active human papilloma virus (genotype 16 and 18) through causing dysplasia may induce cancer [9].

Notwithstanding the issues of cost and unconvincing survival benefit of a surveillance strategy—it is still advocated by the American and British Societies of Gastroenterology.

American Guidelines [2]

1. Every 3–5 year for no dysplasia
2. Every 6–12 month for low grade dysplasia
3. Every 3 months for high grade dysplasia. This group should be considered for endoscopic treatment. Unwilling patients can remain on surveillance.

British Guidelines

1. Barrett's less than 3 cm without intestinal metaplasia or dysplasia should be re-endoscoped and biopsied.
   If no metaplasia, no surveillance
   If metaplasia detected, surveillance should be done every 3–5 years.
2. Barrett's 3 cm length should have surveillance every 2–3 years.
3. For low grade dysplasia, surveillance every 6 months.
4. For high grade dysplasia endoscopic therapy should be offered.

Newer developments in endoscopic technology if incorporated in the surveillance programme can further improve the diagnostic yield. Its cost-effectiveness will remain an issue. The benefits of narrow band imaging (NBI), High Definition White Light Endoscopy (HD-WLE) and Endoscope based Confocal Laser Endomicroscopy (CLE) have already been published. One study has shown NBI to have higher detection rate than HD-WLE (30% v. 21%) [10]. In yet another study ECLE has been shown to have higher neoplasia detection rate than HD-WLE (34%–7%) [11]. In view of the above discussion what is important is to identify the high risk patients for surveillance. It will be appropriate to incorporate the newer technologies in this regard. Cost will, nonetheless, remain an issue.

Gastric Intestinal Metaplasia

Carcinoma of the stomach progresses through inflammation causing metaplasia and dysplasia. Upto 10% of patients with gastric intestinal metaplasia develop carcinoma of the stomach [12]. This calls for a surveillance programme. Unfortunately except in Japan (with high incidence) it has not been found to be cost-effective in most countries. It is thus felt that risk stratification may help downsize the population for effective surveillance. What are these risk factors? Site, size and severity of metaplasia are some of them. Gastric body lesions have a higher chance of developing cancer. Diffuse intestinal metaplasia in antral area or lesser curvature too has a higher risk [13].

Guidelines for surveillance for gastric intestinal metaplasia, as proposed by the European Society of Gastrointestinal Endoscopy, [14] include:

- Extensive metaplasia of the antrum and body every 3 years
- At least 4 biopsies from the proximal and distal stomach, from lesser curve and greater curve.
- Intestinal metaplasia of the antrum alone does not need surveillance
- Low grade dysplasia without a demonstrable lesion should have re-endoscopy after 1 year
- If endoscopy reveals any lesion it should be resected.
- Only dysplasia without a lesion should be followed up with repeat endoscopy.

For purposes of surveillance, biopsy under while light endoscopy (WLE) is currently used. Since CLE offers higher magnification, it is being increasingly favoured [15]. Initially HD-WLE is done to identify an abnormal lesion followed by chromoendoscopy for the same purpose. Next, CLE is done to further access the lesion biopsying these if high grade dysplasia or early cancer is suspected [16].

Polyps of the Colon and Rectum

Two different types of polyps occur in the colon and rectum—adenomatous and hyperplastic. The former (adenomatous polyp) are long known to progress into carcinoma and are responsible for 70% of colorectal cancer. These polyps can be tubular, tubulovillous or villous. The risk of malignancy in these polyps is related to their number, size and histological evidence of dysplasia. Based on these, polyps can be low risk (one or two, less than 1 cm in size) or high risk (3 or more lesions, larger than 1 cm and villous adenoma) [17]. Hyperplastic polyps, though not considered premalignant in the past, are now considered serrated polyps and have been considered to be associated with cancer in 20%–35% of cases. This is related to methylation of CPG, BRAF mutation with inactivation of MLH1 leading to microsatellite instability. The incidence of serrated polyps is reported to vary between 2% and 70% [18].

Following are the Guidelines [19] of the American Gastroenterology Association for surveillance of serrated colorectal polyps:

1. Serrated polyp <1 cm without dysplasia: surveillance every 5 years.
2. Serrated polyp upto 1 cm with dysplasia: surveillance interval at 3 years.

3. At least 5 serrated polyps above the sigmoid colon with history of serrated polyp in family and polyps more than 20 irrespective of the site: surveillance every year.

While discussing surveillance for colorectal cancer, note has to be made regarding interval cancer defined as development of cancer between two surveillance colonoscopies. This happens due to (i) a missed polyp on the previous occasion, (ii) incomplete removal of a polyp—residual one turning malignant, and (iii) new lesion occurring in the intervening period. These interval cancers are biologically different from non-interval cancers. Interval cancers have microsatellite instability, CPG methylation, low Kirsten rat sarcoma viral oncogene (k-ras). These are common, as mentioned earlier, in serrated polyps [20].

In this setting also, newer technologies involving HD-WLE for low risk population, NBI, and chromoendoscopy for serrated polyps and suspected Lynch syndrome have been recommended by the European Society of Gastroenterology [21]. Even CLE and autofluorescence have been suggested in one study [22].

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Feeding a Patient in ICU

Importance of nutrition (feeding) in a sick patient admitted in ICU is now well recognized. But the practice guideline is still not universally defined. Even if there is one – it is controversial and unclear [1]. Most consider providing nutrition as part of care but few consider this for its potentially therapeutic benefit. When to start feeding and what should be fed are currently debated. These aspects are reviewed in this section.

When to Start?

Should it be early or late? The decision is largely opinion based and not based on results of any clinical trial. How early is early to start nutrition is another vexed issue. While some advise 24 hours others believe 48 hours after intubation in ICU is the earliest time to start nutrition. Two different meta-analysis have shown reduction in mortality [2, 3] with early feeding within 24 hours. The first study also demonstrated reduction of pneumonia in those patients. This study, however, did not show any reduction in multi-organ failure [2]. Two more recent studies defined early feeding as within 48 hours of acute illness. None of these studies showed reduction in mortality [4, 5]. The issue of 24 hours and 48 hours as the definition of 'early' feeding thus continues to be debated. Within this diverse result, one can only say that starting nutrition within 48 h can be defined as 'early'. As of now no study exists which compares results of feeding starting at 24 hours and 48 hours – it is desirable that such a study is initiated to address the issue properly.

Should It Be Enteral or Parenteral Nutrition?

The problem of enteral feeding in a sick patient in the ICU is the concern of gut ischaemia (particularly when associated with hypotension), delayed gastric emptying (gross gastric residue), risk of aspiration pneumonia, presence of paralytic ileus and not infrequently non-availability of suitable access of feed delivery. In view of all these problems of enteral feeding, parenteral nutrition has been advised by many a specialist. It thus became a ready source of nutrition (quite often supplementing enteral feeding). It can deliver the necessary caloric needs of a patient when enteral feeding can not be achieved in critically ill patients. This does not undermine the value of enteral nutrition. In fact, whenever possible one should provide enteral nutrition because it can stimulate brush border enzymes necessary for absorption. Enteral feed effectively maintains or increases immunity and prevents bacterial translocation. It also maintains integrity of the intestinal epithelium including height of microvilli [7]. Thus, it is only when enteral feeding is not possible or when adequate calorie supplementation is not possible through enteral feeding, one should consider parenteral nutrition. In fact European guidelines recommend this strategy

[8]. The American guideline too recommends this, the difference being that it defers parenteral therapy after 1 week [9]. The issue of supplemental parenteral nutrition at days 2 and 8 has been studied by Casaer et al. [4]. They concluded that recovery was faster with fewer complications with later therapy than early one. They recommended only glucose infusion initially and adding protein and lipids gradually over a period of time. A subsequent analysis of the same study had however shown detrimental effects of both excessive enteral and parenteral feeding initiated from days 3–7. In fact it was shown that patients receiving excess feeding (day 3 through day 7) are unlikely to leave ICU alive [10].

What If Patients Can Not Tolerate Enteral Feeding?

Cahill et al. [6] conducted an observational study on early parenteral nutrition when enteral feeding could not be established and reported its beneficial effects. However, in a more recent study in 2013, Doig et al. [11] have reported just the reverse. One may question the methodology of this particular study but the focus should not be lost because the benefit is not convincing.

What Should Be the Amount of Enteral Nutrition?

It has repeatedly been emphasized that enteral feeding is good but no one has shown the exact quantity of enteral feeds which can be safely delivered. Only recently, some light has been thrown on the subject. One study [12] has compared trophic feeds (early low dose enteral feed-given at a rate of 10 ml/hours) and early full calorie feed (25 ml/hours with increment every 6 hours until total calorie needs are met) given for the first 6 days of intubation. This study did not find any significant difference in clinical outcome. ICU stay, ICU death and ventilator withdrawal remain same in both groups.

The EDEN study which adopted a similar protocol in a large randomized trial failed to show any difference in mortality, infection and ventilator free life between the two groups [5]. Nearly 50% of these patients were available for follow up at 6 months and 12 months. Long term results evaluated were cognitive domain and physical strength following trophic and full calorie feeds. There was no difference in either in both the arms [13]. Based on the currently available evidence one can conclude that nutrition should be started within 48 hours of intubation in the ICU. Enteral nutrition should be used in the beginning. If enteral feed is not tolerated or not possible, one can supplement with parenteral nutrition. For enteral feeding trophic feed is preferred as the full calorie feed does not have any extra benefit.

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