Peptic Ulcer Disease

Dyspepsia is an umbrella term used to describe a range of symptoms associated with the upper gastro-intestinal tract and includes: upper abdominal pain or discomfort, heartburn, acid reflux, nausea and vomiting.

The most common causes of dyspepsia are:

-Non-ulcer or functional dyspepsia,

-GORD and

-Peptic ulcer

An ulcer is defined as a breach in the gastric or duodenal mucosa down to the submucosa.

Pathophysiology of peptic ulcer:

There are two common forms of peptic ulcer disease:

- Those associated with the organism ***H. pylori*** and
- Those associated with the use of aspirin and **NSAIDs**.

Less common is ulcer disease associated with massive hypersecretion of acid which occurs in the rare gastrinoma (Zollinger–Ellison) syndrome.

Helicobacter pylori

- This organism is a Gram-negative microaerophilic bacterium found primarily in the gastric antrum of the human stomach.
- 95% or more of duodenal ulcers and 80–85% of gastric ulcers are associated with *H. pylori*.
- Transmission most likely occurs via the oral-oral and faeco-oral route.
- Only about 15% of infected individuals develop ulcers. This is likely to be due to variation in virulence between strains of *H. pylori*, differences in host response to infection and other environmental factors.

The underlying pathophysiology associated with *H. pylori* infection involves:

- Production of cytotoxin-associated gene A (CagA) proteins and vacuolating cytotoxins which activate the inflammatory cascade.

- Enzymes produced by H. pylori may cause tissue damage include: UREASE, haemolysins, neuraminidase and fucosidase.
- Gastrin homeostasis is also altered resulting in Long-standing hypergastrinaemia leads to an increased parietal cell mass.
- All these cause inflammation and ulcer formation.

Non-steroidal anti-inflammatory drugs

- The major systemic action of NSAIDs that contributes to the formation of ulcers is the reduction of mucosal **prostaglandin** production via COX-1.
- This leads to a reduction in the mucosal protective mechanisms of mucous, bicarbonate production and mucosal repair.
- Patients taking NSAIDs have a four-fold increase in the risk of ulcer complications compared with nonusers.

- The risk of ulcer complications is progressive depending on the number of risk factors present in the patient… (see Box 12.1) The most important **risk factors** are a history of ulcer complications and advancing age, particularly older than 75 years. Corticosteroids alone are an insignificant ulcer risk but potentiate the ulcer risk when added to NSAIDs, particularly in daily doses of at least 10 mg of prednisolone.
- NSAIDs differ in their propensity to cause ulceration, with **ibuprofen** and **diclofenac** considered lowest risk, and ketoprofen and azapropazone considered highest. The risk also increases with higher doses of NSAIDs.

Box 12.1 Risk factors for NSAID ulcers

Age greater than 65 years
Previous peptic ulceration/bleeding
High dose of NSAID or more than one NSAID (including aspirin)
Short-term history of NSAID use (<1 month)
Concomitant corticosteroid or anticoagulant use
Cardiovascular disease

Selective cyclo-oxygenase-2 inhibitors

The gastro-intestinal side effects of conventional NSAIDs are mediated through the inhibition of COX-1. COX-1 stimulates synthesis of homeostatic prostaglandins while COX-2 is predominantly induced in response to inflammation. Selective COX-2 inhibitors tend not to reduce the mucosal production of protective prostaglandins to the same extent as NSAIDs. COX-2 inhibitors are, therefore, considered to be safer than non-selective NSAIDs in patients at high risk of developing gastro-intestinal mucosal damage.

Zollinger–Ellison syndrome

Zollinger–Ellison syndrome is a rare syndrome that consists of a triad of non-β islet cell tumours of the pancreas that contain and release gastrin, leading to gastric acid hypersecretion and severe ulcer disease. Extrapancreatic gastrinomas are also common and may be found frequently in the duodenal wall.

Patient assessment and clinical manifestations

- Typical symptoms for the underlying causes of dyspepsia are lack specificity and, alone, are poor indicators of the underlying cause.
- Patients with ‘undiagnosed’ dyspepsia, need assessment for **ALARM features** (see Box 12.3) and Medication used (Box 12.4).
- Peptic ulcers classically present with **epigastric pain**, described as a **gnawing or burning** sensation, although some ulcers (particularly NSAID-induced ulcers) are asymptomatic. **Duodenal ulcers** typically cause pain occurring 1–3 hours after meals, which is **relieved** by food, whereas **gastric ulcer** pain is typically **triggered** by food.
- **Complications** of peptic ulcer disease may occur with or without previous dyspeptic symptoms. These are haemorrhage (haematemesis or melaena), chronic iron-deiciency anaemia, pyloric stenosis and perforation. In the setting of acute gastrointestinal bleeding with significant blood loss, patients may present with tachycardia and hypotension.

Box 12.4 Alarm features

Dysphagia
Pain on swallowing
Unintentional weight loss
Gastro-intestinal bleeding or anaemia
Persistent vomiting
On NSAIDs or warfarin

Box 12.3 Drugs causing dyspepsia

Antibiotics
Bisphosphonates
Calcium channel blockers
Corticosteroids
Drugs with antimuscarinic effects, for example, tricyclic antidepressants
Iron
Nitrates
NSAIDs including aspirin
Potassium chloride
Theophylline

Investigations

Endoscopy

- Endoscopy is generally the investigation of choice for diagnosing peptic ulcer, and the procedure is sensitive, specific and safe. However, it is also invasive and expensive.
- Endoscopic investigation should be undertaken in patients with ALARM FEATURES and in those patients over 55 years who present with unexplained or persistent symptoms of dyspepsia (Most patients do not require endoscopy and in those at low risk).
- Biopsies may be taken to exclude malignancy and uncommon lesions such as Crohn's disease.

Radiology

- Double-contrast barium radiography should detect 80% of peptic ulcers.
- Less accuracy and less preferred compared with endoscopy.

H. pylori detection

There are several methods of detecting *H. pylori* infection:

- **Non-invasive tests**: serological tests to detect antibodies, [13C] urea breath tests and Stool antigen tests.
- **Invasive test**: requiring gastric antral biopsies.

Urea breath tests have a sensitivity and specificity over 90% and are accurate for both initial diagnosis and confirmation of eradication. The breath test is based on the principle that urease activity in the stomach of infected individuals hydrolyses urea to form ammonia and carbon dioxide. The test contains carbon-labelled urea which, when hydrolysed, results in production of labelled carbon dioxide which appears in the breath test is preferable and more convenient.

Serological tests are based on the detection of anti-*H. pylori* IgG antibodies but are not able to distinguish between active or previous exposure to infection. Near patient serology tests are not recommended as they are inaccurate.

The stool antigen test uses an enzyme immunoassay to detect *H. pylori* antigen in stool. This test also has a sensitivity and specificity over 90% and can be used in the initial diagnosis and also to confirm eradication.

Treatment of peptic ulcer disease

Acute Bleeding peptic ulcer

- Most patients with bleeding peptic ulcer are clinically stable and stop bleeding without any intervention, whereas other outcomes include re-bleeding and mortality.
- **Endoscopy** allows identification of the severity of disease as well as endoscopic haemostatic therapy which is successful in reducing mortality. A number of pharmacological agents have been used for endoscopic injection therapy such as 1:10,000 **adrenaline** (epinephrine), human thrombin and fibrin glue.
- **Mechanical endoscopic** treatment options include thermocoagulation using a heater probe or endoscopic clipping.
- **Combination therapies** are superior to monotherapy and a combination of adrenaline 1:10,000 with either thermal or mechanical treatment is recommended.
- **Surgery**, to reduce re-bleeding rates and mortality, but bleeding recurs in about 10% of patients and can cause death.
- Patients with uncontrolled bleeding should receive repeat **endoscopic** treatment, **arterial embolization** or surgery.
- **Acid suppression** reduces the re-bleeding rate and should be given to those patients at high risk of re-bleeding following endoscopic haemostatic therapy. The rationale for this is based on the fact that gastric acid inhibits clot formation and if intragastric pH is maintained above

6 during the first 3 days after the initial bleed, there is opportunity for clot stabilization and haemostasis.

- High dose **PPI therapy** is given (e.g. 80 mg bolus omeprazole, pantoprazole or esomeprazole followed by 8 mg/h for 72 h) following endoscopic haemostasis.
- Successful **eradication of *H. pylori*** reduces the rate of re-bleeding to a greater extent than antisecretory non-eradicating therapy.

Uncomplicated peptic ulcer disease

H. pylori eradication

It is known that *H. pylori* infection is associated with over 90% of duodenal ulcers and 80% of gastric ulcers. Cure of this infection with antibiotic therapy and simultaneous treatment with conventional ulcer-healing drugs facilitates symptom relief and healing of the ulcer and reduces the ulcer relapse rate. Antibiotics alone, or acid-suppressing agents alone, do not eradicate *H. pylori*. Both therapies act synergistically as growth of the organism occurs at elevated pH and antibiotic efficacy is enhanced during growth. Additionally, increasing intragastric pH may enhance antibiotic absorption.

The standard regimen is a triple therapy consisting of a PPI, clarithromycin and amoxicillin (or metronidazole), Dose: Twice daily for 1-2 weeks.

Failure of a first-line regimen to achieve eradication will necessitate treatment with another triple therapy regimen, **PPI, amoxicillin (or tetracycline) and metronidazole**. Or switch to Quadruple therapy regimens, the most common is **bismuth subsalicylate, metronidazole, tetracycline (or amoxicillin) and PPI.** Quadruple therapy generally not as well tolerated by patients as triple therapy regimens.

H. pylori eradication for peptic ulcer disease should be confirmed 6–8 weeks after beginning treatment by retesting. If first- and second line regimens fail, gastric biopsy and sensitivity testing are recommended.

If eradication is successful, uncomplicated active peptic ulcers heal without the need to continue ulcer-healing drugs beyond the duration of eradication therapy.
Patients with persistent symptoms after eradication therapy should have their *H. pylori* status recheked. This should be carried out no sooner than 4 weeks after discontinuation of therapy to avoid false-negative results due to suppression rather than eradication of the organism. If the patient is *H. pylori* positive, an alternative eradication regimen should be given. If eradication was successful but symptoms persist, gastro-oesophageal reflux or other causes of dyspepsia should be considered.

Table 12.3 *Helicobacter pylori* eradication first-line regimens	
Standard (7 days)	PPI twice a day, amoxicillin 1 g twice a day, clarithromycin 500 mg twice a day Or PPI twice a day, amoxicillin 1 g twice a day metronidazole 400 mg twice a day
Penicillin allergy (7 days)	PPI twice a day, clarithromycin 250 mg twice a day, metronidazole 400 mg twice a day
Penicillin allergy and previous clarithromycin exposure	PPI twice a day, tripotassium dicitratobismuthate (De-nol) 240 mg four times a day[a] tetracycline 500 mg four times a day, metronidazole 400 mg twice a day

Table 12.4 *Helicobacter pylori* eradication second-line regimens	
Standard (use whichever was not used first line)	PPI twice a day, amoxicillin 1 g twice a day, clarithromycin 500 mg twice a day Or PPI twice a day. amoxicillin 1g twice a day, metronidazole 400 mg twice a day
Previous clarithromycin and metronidazole exposure	PPI twice a day, quinolone twice a day, tetracycline 500 mg twice a day
Penicillin allergy with no previous quinolone exposure	PPI twice a day, metronidazole 400 mg twice a day, levofloxacin 500 mg twice a day
Penicillin allergy with previous quinolone exposure	PPI twice a day, tripotassium dicitratobismuthate (De-nol) 240 mg four times a day,[a] tetracycline 500 mg four times a day, metronidazole 400 mg twice a day

NSAID-associated ulcers

Treatment

If NSAIDs are discontinued, most uncomplicated ulcers heal using standard doses of a PPI, H2-receptor antagonist, misoprostol or sucralfate. Healing is impaired if NSAID use is continued. Studies have demonstrated conflicting results about healing rates between PPIs and H2-receptor antagonists, PPIs demonstrate higher healing rates at 4 weeks but similar healing rates to H2-receptor antagonists at 8 weeks. There is no evidence that high-dose PPI is better than treatment with the standard dose. Although effective, misoprostol use is limited by treatment-related adverse events.

Prophylaxis

NSAIDs should be avoided in patients who are at risk of gastro- intestinal toxicity. However, some patients with chronic rheumatological conditions may require long-term NSAID treatment, in which case the lowest effective dose should be used.

Treatment options for ulcer prophylaxis in patients at risk of peptic ulcer but who require NSAIDs, include co-therapy with acid-suppressing agents or a synthetic prostaglandin analogue, or substitution of a selective COX-2 inhibitor for a non-selective NSAID.

Ulcer-healing drugs

Proton pump inhibitors

- The PPIs are inactive prodrugs that are carried in the bloodstream to the parietal cells in the gastric mucosa. The prodrugs readily cross the parietal cell membrane into the cytosol. These drugs are weak bases and therefore have a high affinity for acidic environments.

- Under these acidic conditions the prodrugs are converted to their active form, which irreversibly binds the proton pump, inhibiting acid secretion.
- The different PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) bind to different sites on the proton pump, which may explain their differences in potency on a milligram per milligram basis.
- PPIs require an enteric coating to protect them from degradation in the acidic environment of the stomach. This delays absorption and a maximum plasma concentration is reached after 2–3 h.
- Since these drugs irreversibly bind to the proton pump they have a sustained duration of acid inhibition which does not correlate with the plasma elimination half-life of 1–2 h. The apparent half-life is approximately 48 h. This prolonged duration of action allows once-daily dosing of PPIs, although twice-daily dosing is recommended in some cases of erosive oesophagitis.
- All PPIs are most effective if taken about 30 min before a meal as they inhibit only actively secreting proton pumps. Meals are the main stimulus to proton pump activity. The optimal dosing time is 30–60 min before the first meal of the day.

H2-receptor antagonists

- The H2-antagonists are all structural analogues of histamine. They competitively block the histamine receptors in gastric parietal cells, thereby preventing acid secretion. Pepsinogen requires acid for conversion to pepsin and so when acid output is reduced, pepsin generation is, in turn, also reduced.
- All the available drugs (cimetidine, ranitidine, famotidine, nizatidine) have similar properties.
- Maximum plasma concentration is reached within 1–3 h after administration. First-pass hepatic metabolism varies, ranitidine being most extensively metabolised which explains the difference between the intravenous and oral dose.
- All H2-antagonists are eliminated to a variable and significant extent via the kidneys, and all require dosage reduction in moderate-to-severe renal impairment.
- Their main role is in the empirical management of dyspepsia symptoms. If patients with mild symptoms gain adequate relief, it is not necessary to use a PPI. H2-receptor antagonists are preferred over PPIs in the second-line treatment of heartburn in pregnancy, although (there is growing evidence to support safe use of PPIs in those not controlled by H2-receptor antagonists).
- H2-receptor antagonists are less effective than PPIs in treating ulcers when NSAIDs are continued, and in prophylaxis of NSAID-induced ulcers. H2-receptor antagonists do effectively heal ulcers in patients who discontinue their NSAID.
- H2-receptor antagonists are not effective in healing oesophagitis, (this is because H2-receptor antagonists equally effective at suppressing daytime and nocturnal acid secretion. The evening dose of a H2-antagonist is particularly important because during the daytime, gastric acid is buffered for long periods by food; however, during the night this does not occur and the intragastric pH may fall below 2.0 for several hours. For healing oesophagitis, intragastric pH must remain above 4.0 for 18 h or more per day).

Table 12.3 Common adverse reactions to ulcer-healing drugs

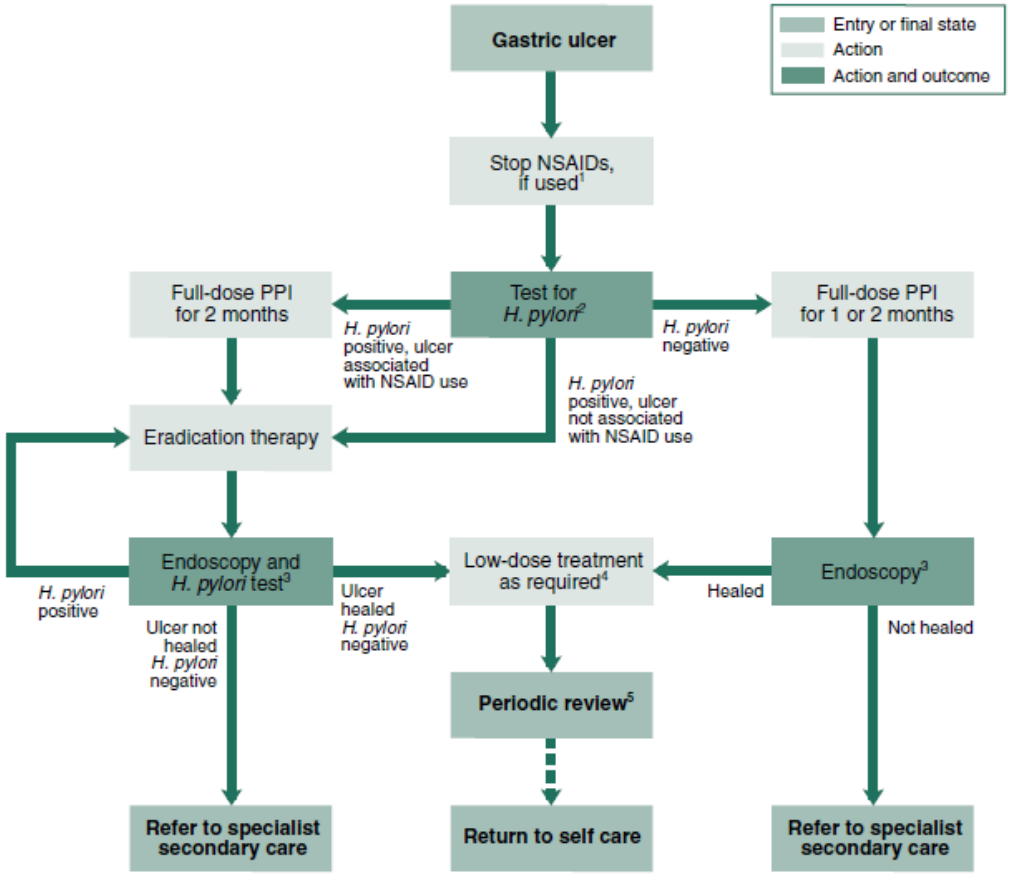
Proton pump inhibitors	H_2-receptor antagonists	Sucralfate
Diarrhoea	Diarrhoea	Constipation
Headache	Headache	
Abdominal pain	Abdominal pain	
Nausea	Confusion	
Fatigue		
Dizziness		

Bismuth chelate

- Bismuth has been included in antacid mixtures for many decades but fell from favour because of its neurotoxicity.
- Its mode of action is not clearly understood but it is thought to have cytoprotective properties. Bismuth is toxic to *H. pylori* and was one of the first agents to be used to eradicate the organism and reduce ulcer recurrence.

Sucralfate

- Sucralfate has no acid-suppressing activity.
- It has mucosal protective effects including stimulation of bicarbonate and mucus secretion and stimulation of mucosal prostanoids.
- At pH less than 4.0 it forms a sticky viscid gel that adheres to the ulcer surface and may afford some physical protection. It is capable of adsorbing bile salts.
- At a dose of 2 g twice daily, sucralfate is effective in the treatment of NSAID-induced duodenal ulcers, if the NSAID is stopped (it is not effective in the treatment and prevention of NSAID-related gastric ulcers).



A

1 If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer COX-2-selective NSAID.

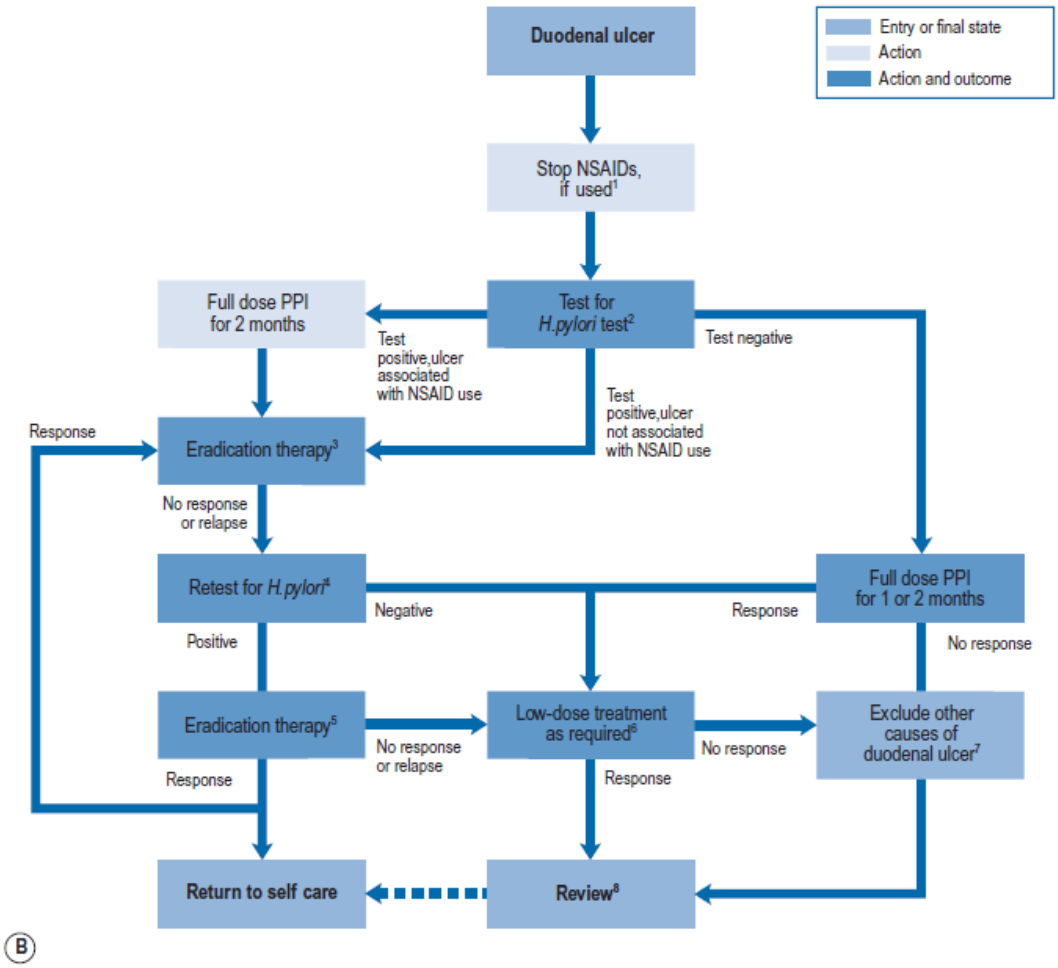
2 Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.

3 Perform endoscopy 6 to 8 weeks after treatment. If re-testing for *H. pylori* use a carbon-13 urea breath test.

4 Offer low-dose treatment, possibly used on an as-required basis, with a limited number of repeat prescriptions.

5 Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice. In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist.

Fig. 12.5 (A) Management algorithm for gastric ulcer. (B) Management algorithm for duodenal ulcer (NICE, 2014a.). (With permission from NICE.)
NSAID, Non-steroidal anti-inflammatory drug.



1 If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer COX-2-selective NSAID.
2 Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.
3 Use a proton pump inhibitor (PPI), amoxicillin, clarithromycin 500 mg (PAC_{500}) regimen or a PPI, metronidazole, clarithromycin 250 mg (PMC_{250}) regimen.
4 Use a carbon-13 urea breath test.
5 Follow guidance found in the *British National Formulary* for selecting second-line therapies.
6 Offer low-dose treatment, possibly used on an as required basis, with a limited number of repeat prescriptions.
7 Consider: non-adherence with treatment, possible malignancy, failure to detect *H. pylori* infection due to recent PPI or antibiotic ingestion, inadequate testing or simple misclassification; surreptitious or inadvertent NSAID or asprin use; ulceration due to ingestion of other drugs; Zollinger-Ellison syndrome, Crohn's disease.
8 Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice.

Fig. 12.5, cont'd (B) Management algorithm for duodenal ulcer.

Reference:
Clinical pharmacy and therapeutics, 6th edition, 2019