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COVID 19 and the risk of gastro-intestinal perforation:
A case series and literature review

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Abstract

Keywords:
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Background: COVID19 is a viral disease with pneumonia as its most common presentation. Many presentations and complications have been reported, but gastro-intestinal perforation has not received much attention.

Methods: three cases from our hospital are presented, and the current literature was reviewed.

Results, cases: All three patients were admitted to the ICU with respiratory failure due to COVID19 pneumonia and intubated. Our first patient was treated with steroids, and subsequently diagnosed with rectal perforation on day 34 of his hospital admission. The second patient was treated with steroids and tocilizumab, and diagnosed with colonic perforation 1 day after neostigmine administration, on day 14 of his hospital admission. Our third patient was treated with steroids and tocilizumab, and diagnosed colonic perforation 4 days after neostigmine administration, on day 14 of his hospital admission.

Results, literature: 25 more cases were found in current literature, both upper GI and lower GI perforations, either as a presenting symptom or during the course of hospitalization. These were often associated with treatment with steroids, interleukin 6 inhibitors, or both.

Conclusions: Gastro-intestinal perforation is a rare but dangerous complication of COVID19. Treatment with tocilizumab and steroids may both increase the risk of this complication, and hamper diagnosis.

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1. Cases

We present three cases of colorectal perforation in patients with COVID 19, two of which previously treated with steroids and tocilizumab.

A 65 year old male with a history of percutaneous coronary revascularization was admitted to our ICU with COVID 19 pneumonia, and intubated on day 5, for respiratory failure. From day 16 on he had recuring fevers despite multiple antibiotics. Prednisolone was started on day 22: 120 mg daily for five days, then tapered over 19 days. On day 28 rectal bleeding was noticed, a lower rectum perforation with perirectal abscess was diagnosed on day 34. A diverting colostomy was performed. He was discharged from the ICU on day 49. His ICU treatment was complicated by an ischemic stroke, hampering his recovery. He was discharged to a rehabilitation facility on day 90. Last follow-up was on day 370, patient has returned home but has not yet fully recovered. Imaging and endoscopy suggest the defect has fully healed, restoration of intestinal continuity is under consideration.

A 58 year old male with a history of mild obesity was transferred to our ICU with COVID 19 pneumonia. He was intubated and received dexamethasone 6 mg/day continued for 19 days, starting one day previous to intubation. He also received tocilizumab (8 mg/kg, on day of intubation). On day 13, neostigmine was administered (2 mg/h for 24 h) because of increasing abdominal distension and failure to pass stool, with rapid result. On day 14 a CT scan of the chest and abdomen (performed to rule out pulmonary embolus) showed a distended caecum and marked intraperitoneal air, without free fluid or signs of focal inflammation. Because of a lack of sepis, and a high risk of worsening his pulmonary status with surgery, we initially opted for a diagnostic peritoneal lavage, which was negative. 36 h later he developed signs of sepis, and a repeat CT showed increased free air, and focal inflammation of the caecal region. Exploratory laparotomy showed perforation of focal necrosis/ischemia of the caecum. Llooaecetomy was performed, and an end-ileostomy created. He was extubated 10 days...

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Table 1

| Author / Case | Period / Age | Time of perforation | IL antagonist | Steroids | Location | Specifics | Treatment | outcome |
|---------------|--------------|---------------------|---------------|----------|----------|----------|-----------|---------|
| Lower GI perforation |
| Nahas (6) | 1 / 92 | Before COVID diagnosis | none | None | Transverse colon | 5 days postoperative after colostomy for obstructive rectal cancer | Resection | Deceased |
| Giuffre / A (4) | 1 / 87 | Before hospital admission | none | None | Lower rectum | Conservative | Deceased |
| Santana (7) | 2 / 43 | Before hospital admission | none | none | Terminal ileum | Medical history of crohn’s disease | Resection | Recovered |
| Costanzi (3) | 2 / 64 | Before hospital admission | none | none | Sigmoid | Diverticulitis | Resection | Recovered |
| Verma / B (8) | 2 / 24 | After hospital admission | none | none | Coecum | 5 days post caesarean section | Primary closure and defunctioning ileostomy | Recovered |
| Neto (2) | 1 / 80 | Before hospital admission | none | None | Sigmoid | Resection | Recovered |
| Bulit / A | 1 / 65 | After ICU admission | Dexamethasone tapering dose | Prednisolone | Mid rectum | Defunctioning colostomy | Resection | Recovered |
| Baiu (1) | 2 / 66 | Before hospital admission | none | Dexamethasone | Coecum | After clostridium difficile infection | Resection | Recovered |
| Verma / A (8) | 2 / 60 | Before hospital admission | none | ‘steroids’ | Upper rectum | Primary closure and defunctioning colostomy | Resection | Recovered |
| Bulit / B | 3 / 58 | After ICU admission | Methylprednisolone 6 mg/kg daily | Tocilizumab | Coecum | Neostigmine use, very distended ascending colon | Resection | Discharged to rehabilitation facility |
| Bulit / C | 3 / 57 | After ICU admission | Methylprednisolone 6 mg/kg daily | Tocilizumab | Transverse colon | Neostigmine use | Resection | Recovered |
| Rojo (18) | 1 / 54 | After ICU admission | Methylprednisolone | Tocilizumab | Ascending colon | Resection | Deceased |
| Bruce-Hickman (20) | 1 / 43 | After ICU admission | Methylprednisolone 100 mg (previously) | Tocilizumab | Coecum | After embolization of bleeding ulcer | Resection | NR b |
| Guardiola (16) | 2 / 66 | After ICU admission | Methylprednisolone 1 mg/kg/day | Tocilizumab | Ascending colon | Resection | NR b |
| Montorfano (17) | 1 / 54 | After ICU admission | Methylprednisolone 2 mg (single dosage) | Tocilizumab | Coecum | Resection | Discharge to long-term care facility |
| De Nardi (10) | 1 / 53 | After ICU discharge | Anakinra | Tocilizumab | Coecum | Very distended ascending colon | Resection and anastomosis | Resection |
| Schwab (19) | 2 / 34 | After ICU admission | IL-6 receptor agonist | Tocilizumab | Coecum | Resection | Deceased |
| Giuffre / B (5) | 1 / 68 | After hospital admission | NR b | Not reported | Rectum | Conservative | Deceased |
| Giuffre / C (5) | 1 / 84 | After hospital admission | NR b | None | Rectum | Conservative | Deceased |
| Bhayana (9) | 1 / NR b | After hospital admission | NR b | NR b | Ileum | NR b | NR b |
| Upper GI perforation |
| Verma / C (8) | 2 / 21 | Before hospital admission | NR b | None | Stomach | Primary closure and graham patch | Recovered |
| Kangas (13) | 1 / 74 | After ICU admission | none | None | Presumed upper GI | Refused surgery | Conservative | Deceased |
| Lee (15) | 1 / 73 | After hospital admission | none | None | Duodenum | After embolization of a bleeding ulcer | Primary closure, pyloric exclusion and gastrojejunostomy | Recovered |
| He (12) | 1 / 71 | After hospital admission | none | None | Duodenum | Primary closure | Recovered |
| Marcucci (14) | 1 / 71 | After ICU admission | none | None | Stomach | After bag-mask ventilation, large defect | Surgically, not specified | Deceased |
| Galvez (11) | 1 / 59 | After hospital admission | Methylprednisolone 1 mg/kg/day | None | Gastrjejunostal anastomosis | After RYGB | Graham patch repair | Recovered |

(continued on next page)
postoperatively. A perisplenic abscess was drained percutaneously on day 14, he was discharged from the ICU 19 days postoperatively. Histology showed circumscribed ulceration with transmural abscess formation and necrosis.

A 57 year old male with a history of mild obesity was admitted with a COVID 19 pneumonia, and started on dexamethasone, 6 mg/day, continued for 17 days. On day 2 he was admitted to our ICU with impending respiratory failure, and intubated on day 3. He received tocilizumab (8 mg/kg on day 3). Because of increasing abdominal distension and failure to pass stool on day 10, a CT scan was performed to rule out mechanical obstruction. This showed a distended colon and distal small intestine, a small amount of ascites, no free air. Neostigmine was started (2.5 mg/h for 24 h) with rapid result. On day 14 an abdominal CT was performed because of progressive abdominal distension without signs of sepsis, and found a moderately distended caecum, massive intraperitoneal air. Exploratory laparotomy showed a distended proximal colon, fixed to the ventral abdominal wall, with perforation of the distal transverse colon. An extended right hemicolectomy was performed, and an end-ileostomy created. He was extubated two days postoperatively and discharged from the ICU on postoperative day 4. He was discharged to a rehabilitation facility on postoperative day 19. Histology of the colon showed abrupt transitions from normal tissue to non-specific ischemic necrotic changes with a regenerative response. Elective stoma reversal was performed 189 days post initial admission.

2. Discussion

Table 1 shows a number of intestinal perforations in COVID patients have been reported, but considering the worldwide incidence of COVID, this appears to be a rare complication. A review of the literature to date (April 2021) showed a total of 25 gastro-intestinal perforations. We found 18 perforations in patients not treated with IL-6 inhibitors. Of these 18 cases, 12 were lower GI perforations (1-10), 6 were perforated gastroduodenal ulcers (8,11-14). One of these after embolization of a bleeding ulcer (15). Seven cases occurred after treatment with tocilizumab or sarilumab: an additional 5 cases of lower GI perforation (16-19), including one subclinical perforation after embolization of a bleeding ulcer (20). One additional upper GI perforation was found, also after embolization of a bleeding ulcer (21). One was only reported as ‘gastro-intestinal perforation’ (22). When looking at the use of steroids: treatment with steroids was reported in 10 cases. Of these 10 cases, six received concurrent treatment with tocilizumab. Including the present report, 13 patients recovered, 9 patients died, outcome was not reported for 6 patients. While the reporting might very well be biased, prognosis of gastro-intestinal perforation in COVID patients is not abysmal.

Intestinal perforation is a well-known complication of tocilizumab in rheumatoid arthritis, affecting approximately 3/1000 patient years (23,24). Risk is increased with concurrent steroid treatment (24). The pathophysiology of perforation is unknown.

Based on this data in rheumatoid arthritis, when tocilizumab was first used in COVID 19, it was hypothesized that perforation might complicate treatment (25). Our cases and the review of the literature indicate a risk of perforation in COVID19 patients not treated with tocilizumab as well. Whether this association is enhanced by tocilizumab treatment remains unsure.

Perforation complicating neostigmine treatment for Ogilvie’s syndrome has also been reported a few times (26-29). Though there was no evidence of mechanical obstruction in our patients, the use of neostigmine could also have been contributory.

Tocilizumab is increasingly used in the treatment of severe COVID 19, and this is likely to increase further since the publication of the results of the REMAP-CAP trial (401 patients on IL-6 inhibitors, 402 controls) and the RECOVERY trial (2022 patients on tocilizumab, 2094 controls) (30,31). Both studies report only low numbers of serious adverse events, neither study reports any perforations. It is generally combined with steroids, compounding perforation risk. Whenever possible, other risk factors (e.g. the use of neostigmine, colonic instrumentation) should be avoided. While the benefits of tocilizumab may well justify its use in severe COVID19 patients, health care providers should be mindful of potential intestinal perforation in patients with COVID, perhaps even more so when they are also treated with tocilizumab. Specifically: classic signs of abdominal sepsis might not be apparent due to the immunosuppressive nature of tocilizumab and concurrent steroid use. Tocilizumab is a powerful suppressor of CRP, but not leukocytosis (32). This can make it extra challenging to differentiate between gastro-intestinal perforation, and pneumoperitoneum from other causes, e.g. alveolar barotrauma (the Macklin effect) (33,34). Similar to perforation in non-COVID patients, rapid diagnosis and surgical treatment is of the utmost importance, and can lead to favorable outcomes.

Declarations

Ethics approval for case report is not required under Dutch law.

Consent for publication

All included patients consented to the use of their data.

Availability of data and materials

Not applicable.

Competing interests

None.

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None.

Authors’ contributions

JPB: Conceptualization, data curation, formal analysis, writing - original draft and review & editing. NP, MB, BI and AGS data curation,
writing - review & editing. HvdlH took Ceonceptualization, formal analysis, writing - review & editing.

Take home message

Gastro-intestinal perforation is a rare but dangerous complication of COVID19. Treatment with tocilizumab and steroids possibly increase the risk of this complication, and hamper its diagnosis.

Tweet

Gastro-intestinal perforation: a rare but dangerous complication of COVID19. Tocilizumab and steroids possibly increase risk, hamper diagnosis.

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