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NVIC NAJAARSCONGRES

2018

De IC van de lange adem
uitdagingen bij langliggers

Donderdag 13 september 2018
Postillion Hotel Utrecht
Bunnik

Nederlandse Vereniging voor Intensive Care - www.NVIC.nl
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Netherlands Journal of Critical Care is indexed in:
EDITORIAL

It’s not a gut feeling: don’t listen to the bowels

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Keywords - ileus; auscultation; physical examination; enteral feeding

In my 1973 copy of Hamilton Bailey’s Demonstration of Physical Signs in Clinical Surgery it is stated that auscultation of the abdomen is of ‘overriding importance’ in the investigation of ileus, be it obstructive or paralytic.[1] The doctor should be seated on a chair on the right side of the patient’s abdomen, command everybody in the vicinity to be quiet, apply the cup of the stethoscope firmly to the skin just below and to the right of the umbilicus, and listen – if necessary – for three full minutes. Only then can an ileus be diagnosed or the diagnosis can be discarded. In this issue of the Netherlands Journal of Critical Care, Van Bree reports a review of the literature on the utility of auscultation for bowel sounds in clinical decision-making.[2] It may be questionable whether the auscultation in the reported studies was executed as meticulously as prescribed by Hamilton Bailey - in the intensive care unit it will seldom be quiet, even if the doctors these days still have the authority to command silence - but the conclusion is firm: auscultation of the abdomen is useless, should be abandoned, and – most importantly – should not contribute to the process of clinical decision-making.

So, if auscultation of the abdomen does not lead to an impact on clinical decision-making and should be abandoned, could this mean that auscultation in general should be abandoned? Indeed, auscultation of the heart by experienced general practitioners has a sensitivity of only 32% and 44% for diagnosing mild and significant valvular heart disease with specificities of 67% and 69%, respectively.[3] Fifty-two patients admitted to the emergency room with symptoms of lower respiratory tract infection were evaluated by a general internist, a specialist in infectious diseases, and a pulmonologist. Without knowledge of the clinical histories, they performed a chest exam to determine whether the patients had pneumonia.[4] As compared with the gold standard chest radiography, the sensitivity of clinical diagnosis ranged from 47 to 69%, and the specificity from 58 to 75%.

Now that we conclude that auscultation is, to say the least, not a very useful part of physical examination, does this mean that performing a physical examination in general can be discarded? After all, it has low specificity and sensitivity, and for the intensivist ultrasound has become a reliable tool. Ultrasound performs much more accurately than physical examination on diagnosing pathological conditions of the lung (consolidation, pleural effusion, oedema), the heart (global dimensions and function, valve dysfunction, volume status) and the abdomen (gastric retention volume, ileus, intra-abdominal air and fluid). Probably, some medical specialists will have to continue doing direct hands-on examinations, e.g. the neurologist with reflex and sensitivity testing (although even pupillary size, symmetry, and reactivity nowadays can be tested automated by a pupilometer handled by a nurse), but for most specialists physical examination may not contribute to the diagnostic process. Even the surgeon will almost always rely on ultrasound and/or CT scanning of the abdomen instead of following the principles that Henry Hamilton Bailey described.[5]

All in all, following this line of reasoning, physical examination can be abolished - or can it? Of course not. History taking and physical examination have been the cornerstone of medicine since Hippocrates, and even though the diagnostic accuracy of physical examination is low compared with modern methods, it still has many valuable aspects - also for ICU patients. But the focus should change from organ-specific diagnosis to more general results and findings. Physical examination results in an intimate interaction between patient and physician, hopefully increasing the patient’s confidence and trust in the doctor’s abilities and therefore his treatment. A physical examination gives the physician insight into the mental state of the patient (delirium, depression), pain and anxiety, and the patient’s will to fight his disease and help in physical rehabilitation. Observing the patient reveals unwanted patient-ventilator interactions and could lead to relevant adjustments in the ventilator settings. Touching the patient provides relevant
knowledge on the circulation. Although auscultation of the heart is inferior to echocardiography, a (new) murmur could point to a new diagnosis such as endocarditis, an acute mitral valve insufficiency or a ventricular septal rupture. In contrast to ultrasound and CT/MRI, physical examination is always available, is cheap, and might reveal conditions that would otherwise go unnoticed, such as decubitus, an infected catheter, petechiae and so on.

In conclusion, I have gone from auscultation of bowel sounds in patients with an ileus to physical examination in general. Returning to the starting point that auscultation for bowel sounds is useless, we - and our nurses! - should stop doing it. This is in line with existing guidelines: enteral feeding should not be withheld in ICU patients with absent bowel sounds. Together with auscultation of bowel sounds, other rituals which hamper optimal enteral feeding, such as measuring gastric retention volume, are to be abolished as well.

The authors are to be complemented with their research, and expanding on ‘test everything, retain what is good’ it is up to us not only to retain what is good, but to discard what is not good, to begin with rituals that hamper optimal feeding.

Disclosures
The author declares no conflict of interest. No funding or financial support was received.

References
Auscultation for bowel sounds in patients with ileus: an outdated practice in the ICU?

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Keywords - auscultation; bowel sounds; intestinal motility; ileus; bowel obstruction

Abstract
Background: Ileus can be the consequence of multiple factors, including an operation, a side effect of drugs or the result of an obstruction requiring direct operative correction. Although auscultation for bowel sounds is routinely performed in the ICU and a well-established part of the physical examination in patients, its clinical value remains largely unstudied.

Methods: To determine whether auscultation for bowel sounds helps in clinical decision-making in ICU patients with ileus, a literature search of PubMed, Embase and Cochrane was performed to study the diagnostic value of auscultation for bowel sounds.

Results: The inter-observer variability for the assessment of the quantity, volume and pitch of bowel sounds was high, with a moderate inter-observer agreement for discerning postoperative ileus, bowel obstruction and normal bowel sounds (kappa value 0.57). The intra-observer reliability of duplicated recordings for distinguishing between patients with normal bowels, obstructed bowels or postoperative ileus was 54%. No clear relation between bowel sounds and intestinal transit was found. Sensitivity and positive predictive value were low: 32% and 23% respectively in healthy volunteers, 22% and 28% in obstructive ileus, and 22% and 44% in postoperative ileus.

Conclusions: Auscultation with the aim to differentiate normal from pathological bowel sounds is not useful in clinical practice. The low sensitivity and low positive predictive value together with a poor inter- and intra-observer agreement demonstrate the inaccuracy of utilising bowel sounds for clinical decision-making. Given the lack of evidence and standardisation of auscultation, the critically ill patient is more likely to benefit from abdominal imaging.

Introduction
Ileus can be the consequence of multiple factors, including an operation, or medications such as opiates, but can also result from an obstruction that may require direct operative correction. As the pathogenesis of ileus is complex, there are more causes of ileus in intensive care patients such as critical illness itself, ischaemia, diverticulitis and peritonitis, contributing at various times during the development of this entity. Therefore, the decreased propulsive ability in patients with ileus may be broadly classified as caused either by bowel obstruction or intestinal atony/paralysis.

Reported clinical symptoms of ileus include nausea, vomiting, bloating, abnormal or loss of peristaltic bowel sounds, delayed passage of flatus and stool, and inability to progress to an oral diet. Gastrointestinal problems occur frequently and are associated with adverse outcomes in intensive care patients. Different gastrointestinal symptoms and complications may occur in up to 50% of mechanically ventilated patients. Despite this, there is no consensus means for obtaining a precise assessment of gastrointestinal function, and it remains unclear which symptoms most reliably reflect recovery of the gastrointestinal tract in the intensive care unit (ICU).

Clinical parameters to diagnose ileus, such as return of bowel sounds and time to first flatus, may lack accuracy, while other clinical parameters such as nausea, vomiting and tolerance of solid food strongly depend on patient reporting. Thus, it is questionable to what extent these parameters reflect recovery of intestinal motility. Thereby, it may not be surprising that studies assessing ileus have used various clinical parameters as primary outcome measure.
In the ICU, diminished bowel peristalsis and the absence of bowel sounds are common in mechanically ventilated patients receiving sedatives, opiates and/or catecholamines. Data suggest that bowel sounds may be decreased or absent in half of the patients in the intensive care.[16-18] There are contradictory data in the literature about what constitutes normal bowel sounds; however, what is consistent throughout is the reported abnormality of a complete lack of bowel sounds.

Auscultation for bowel sounds is routinely performed in the ICU and a well-established part of the physical examination. Abnormality of a complete lack of bowel sounds; however, what is consistent throughout is the reported abnormality of a complete lack of bowel sounds.

Methods

To identify studies and case series that report on the utility of bowel sounds in clinical decision-making in intensive care patients with ileus, we searched MEDLINE (1950 to September 2017), EMBASE (1980 to Sept 2017, ISI Web of Science (1964 to September 2017), and the Cochrane Library (2005 to September 2017). The following subheadings were used: (“intestinal obstruction” OR “bowel obstruction” OR “ileus”) AND (“auscultation” OR “bowel sounds” OR “gastrointestinal motility” OR “peristalsis” OR “diagnosis” OR “ICU” OR “critically ill”).

The authors independently reviewed the titles and abstracts yielded by this comprehensive search. All titles and abstracts were screened to identify manuscripts for eligibility. Based on the initial screening, selected full-text articles were obtained for second stage screening of the whole article. Randomised controlled trials, prospective and retrospective cohorts and case series were all eligible for inclusion, irrespective of publication status, date of publication and blinding status. Language was limited to English. Quality assessment was done with the methodological index for non-randomised studies (MINORS) checklist.[24]

Results

The search yielded 947 articles. After elimination of irrelevant titles and duplicates, 172 abstracts were evaluated. A total of 21 publications were retrieved for further assessment and finally seven full-text articles were included in the results section of this review. There were no systematic reviews or meta-analyses of randomised controlled trials on this topic.

Accuracy and variability in assessment of bowel sounds in bowel obstruction, healthy controls and in postoperative ileus

Only two studies have determined whether an accurate diagnosis of mechanical small bowel obstruction, postoperative ileus and normal intestinal motility can be made based on bowel sound characteristics (table 1).[25,26] Bowel sounds were recorded for 30 seconds using an electronic stethoscope and were randomly replayed to clinicians of the departments of internal medicine and surgery without providing any clinical information. The clinicians were instructed to categorise the patient recordings as small bowel obstruction, ileus or normal. The study by Gu et al. determined the accuracy of bowel sounds in 9 patients with small bowel obstruction, 7 patients with ileus and 10 healthy volunteers.[25] Recordings of patients with obstructive ileus were correctly labelled in only 42%. However, recordings of healthy volunteers and those of patients with ileus yielded a sensitivity of 78% and 84% respectively. If the physician believed she or he was hearing a bowel obstruction, this had a positive predictive value (PPV) of 72%, while for ileus and normal intestinal motility the PPV was 93% and 54% respectively. The inter-observer agreement was moderate (kappa value 0.57). The subsequent study by Felder et al. was a more elaborate reproduction of the earlier published study by Gu et al. with similar results, but also included the level of training of the clinicians.[26] The study cohort consisted of recordings of bowel sounds of 19 patients with mechanical small bowel obstruction, 156 patients with postoperative ileus and 177 healthy volunteers. A total of 45 recordings were played consecutively to physicians, with 15 of the recordings duplicated. Over 78% of the recordings of

Table 1. Accuracy and inter/intra-observer variability in bowel obstruction, ileus and healthy volunteers

<table>
<thead>
<tr>
<th>Author</th>
<th>Design &amp; MINORS score</th>
<th>Patients</th>
<th>Outcome</th>
<th>Results (%)</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breum, 2015*</td>
<td>Prospective 19</td>
<td>Patients with clinically suspected bowel obstruction: A: Intestinal obstruction (n=37) B: Without obstruction (n=61)</td>
<td>Sensitivity, specificity, PPV and NPV of pathological bowel sounds with respect to intestinal obstruction &amp; inter-observer agreement (median kappa (κ)-value)</td>
<td>- Sens.: 42 - Spec.: 78 - PPV: 48 - NPV: 76 - K-value: 0.29 (low)</td>
<td>- Shorter duration of electronic recordings (25 seconds)</td>
</tr>
</tbody>
</table>

PPV = positive predictive value, NPV = negative predictive value; MINORS = methodological index for non-randomised studies score. The global ideal score is 24: 12 items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate)[24]
obstructive ileus were incorrectly labelled and not recognised as obstructive ileus, yielding a sensitivity of less than 22%. Recordings of healthy volunteers and those of patients with postoperative ileus yielded a sensitivity of just 32% and 22%, respectively. The PPV of bowel obstruction recordings was 28% and for normal and postoperative ileus recordings 23% and 44% respectively. This indicates that when a clinician judged the recording to match obstructive ileus, this was actually true in only 28% of cases. Auditory characteristics (tinkling, high pitched and rushes) in each bowel sound category were highly variable. Of all physicians, 58% reported tinkling as normal bowel sounds. However, high-pitched sounds and rushes, characteristics often associated with small bowel obstruction, were reported in 23% to 73% of normal bowel sounds recordings. High-pitched sounds and rushes were reported to be heard less frequently in the obstructed recordings, 28% and 23%, respectively, than in the normal recordings, 60% and 46%, respectively. For the postoperative ileus recordings, clinicians reported hearing tinkling, high-pitched sounds or rushes approximately one-third of the time. The intra-observer reliability for normal bowel sounds was 59%, for obstructive ileus recordings 51% and for postoperative ileus 56%. The overall intra-observer reliability of duplicated recordings was only 54%.

The question remains whether physicians are able to determine by stethoscope whether bowel sounds are normal in their patients suspected of bowel obstruction. Durup-Dickenson et al. assessed inter- and intra-observer agreement in physicians’ evaluation of quantity, volume and pitch of bowel sounds. A total of 100 physicians were presented with 20 bowel sound recordings in a blinded set-up. The recordings had been made in healthy volunteers and patients in the emergency department presenting with peritonitis or bowel obstruction. Inter-observer agreement regarding pitch, intensity and quantity yielded k-values of 0.19, 0.30 and 0.24 (p<0.0001), respectively, corresponding to slight, fair and fair agreement. With regard to the intra-observer agreement, the probability of agreement was only 0.55, 0.45 and 0.41 for pitch, intensity and quantity respectively, which approximates flipping a coin.[20]

Hyperactive bowel sounds were thought to be useful in diagnosing obstructive ileus, as suggested by a cohort study performed by Bohner et al. in patients presenting with abdominal pain lasting less than seven days, and with no history of abdominal injury including surgery. [27] Investigating which data from history and physical examination may help to exclude bowel obstruction and thereby avoid the additional request of abdominal radiographs, they found that ‘increased’ bowel sounds was one of the six variables with the highest sensitivity to exclude bowel obstruction. However, a more recent study investigating the accuracy of bowel sounds to diagnose obstructive ileus was performed by Breum et al., in which 53 physicians listened to electronically recorded bowel sounds from 98 patients admitted with clinically suspected intestinal obstruction. A low accuracy and low inter-observer-agreement for bowel obstruction was found. [28] Moreover, using a simulation model, Mehmood et al. found that healthcare professionals of the internal medicine department and the ICU had a correct detection rate of hyperdynamic bowel sounds of 50%. [29]

Relationship between bowel sounds and intestinal transit

The presence of audible peristalsis as a sign of intestinal contraction is routinely used in postoperative patients. However, until recently it was not known whether this actually correlates with effective intestinal transit. [30,31] Intestinal transit was analysed by scintigraphy in 60 patients to determine which clinical symptoms best reflect postoperative intestinal motility. [13] Postoperative defecation together with tolerance of solid food proved to be the best clinical composite endpoint of postoperative ileus. This was in accordance with a recent systematic review determining the best clinical endpoint for postoperative ileus. [32] Strikingly, seven patients had developed a major postoperative complication, with paralytic ileus requiring a nasogastric tube. In these patients, the indium-111 tracer had not reached the colon at day 2, demonstrating no significant intestinal propulsive activity. Interestingly, in six out of these seven patients with a paralytic ileus, there was still presence of audible peristalsis (table 2). [33] These data indicate that the reported absence of audible peristalsis poorly reflects postoperative dyssmotility.

Table 2. Auscultation for the presence of bowel sounds audible peristalsis in relation with intestinal transit

<table>
<thead>
<tr>
<th>Postoperative day 2</th>
<th>Auscultation of bowel sounds</th>
<th>n =</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>GC = 0 (paralytic ileus)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>GC &lt; 2 (no recovery of colonic transit)</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>GC ≥ 2 (recovery of colonic transit)</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

In the patients without ileus, the recovery of colonic transit (defined as geometrical centre (GC) of radioactivity ≥ 2) was significantly correlated with clinical recovery.[30]

Discussion

There are practical difficulties in determining whether bowel sounds are hyperactive, hypoactive or truly absent, considering that normal bowel sounds occur intermittently between 5 and 35 times a minute in an irregular pattern. [34-37] The minimum amount of time to auscultate before concluding that no bowel sounds are present varied from 30 seconds to 7 minutes, with most authors advising practitioners to auscultate for at least 5 minutes if no sounds are heard initially. [35,38-41] In addition, bowel sounds demonstrate a large variation in sound distribution and
intensity in healthy subjects. Along with this, the terminology commonly used for normal and pathological bowel sounds is variable and the labelling of bowel sounds is often subjective. [17] Thereby, the diagnostic ability of bowel sounds to discern normal and pathological conditions is not well characterised, and aberrant bowel sounds may be of limited value for the diagnosis of small bowel obstruction.[24] Despite these issues, bowel sounds are claimed to help us develop our differential diagnosis.[16,35,36,39-41,43] However, for a diagnostic test to be of value, it not only has to be well interpretable and accurate but, most importantly, also reproducible.[21] In the study by Felder et al. the intra-observer reliability for normal bowel sounds, obstructive ileus recordings and postoperative ileus was low at 50-60%.[26] This makes it unlikely that the diagnostic value of auscultation increases with the addition of patient history and physical findings. Furthermore, several studies have reported no differences between junior and senior doctors, contradicting the assumption that the diagnostic value of auscultation may be further improved by increasing systematic training.[26,28]

Previous studies have demonstrated low to moderate inter-observer agreement for bowel sounds assessment in various motility disorders.[19,20,22,25,28,44] Variation in the intensity of the volume and pitch of the sound further challenges the clinician trying to determine whether bowel sounds are overly loud or soft. A partial obstruction may provoke a hollow, very high-pitched tinkling sound as a result of liquid and gas accumulating under pressure in the dilated bowel. [41] However, there is no clear evidence that very high-pitched bowel sounds have clinical pertinence.[45]

Besides a lack of accuracy, there are specific conditions in the ICU that may further hamper the utility of auscultating bowel sounds in critical care. Contact precautions are part of the standard care in the ICU to prevent the spread of multidrug resistant bacteria from infected or colonised patients. These precautions include the use of disposable or patient-dedicated simple stethoscopes. As previously demonstrated by Mehmood et al., these low-end stethoscopes perform poorly, hampering reliable auscultation in the ICU. Physicians differ in how long they listen for bowel sounds, and they listen for a shorter time compared with nurses in the ICU. As a result, different conclusions about the presence of normal bowel sounds can be made within the same patient in the same department.[21,29] Had abdominal auscultation not been such a cheap commonly practised investigation, it would probably not have survived in clinical practice for more than 150 years, given the very limited documentation of its clinical value.[24,46] The practice of auscultation therefore appears to be more a reflection of tradition and anecdotal evidence, and begs the question whether it may be better to abandon this routine procedure in order to avoid delayed diagnosis or even misjudgement of patients with suspected bowel obstruction.[28] We are strong supporters of the history and physical exam and advocate for the use of hands, ears, nose and eyes to interpret the patient’s condition. However, intensivists must be progressive, embracing new modalities and letting go of less reliable methods. For example, the bedside ultrasound for the diagnosis of small bowel obstruction might be a more suitable alternative. In line with this, a recent systematic review of the diagnostic modalities used to identify bowel obstruction found ultrasound to be superior to all other modalities.[47] The lack of consensus, standardisation and evidence may encourage educators and physicians in the ICU to discuss the efficacy and utility of this manoeuvre during clinical training. Especially, in an era of expanding diagnostic possibilities,[48] the intensive care patient is more likely to benefit from abdominal imaging than auscultation if the suspicion of an ileus requiring operative intervention arises.[49]

For many years, the dogma was not to give patients any oral or enteral feeds unless bowel sounds were present. However, a number of studies have shown that ileus is not equated with intestinal failure and that bowel function and nutrient-absorbing capacity may be suppressed in patients with ileus, but are not absent.[50] Moreover, the sounds made by the bowel are evidence of contractility, not absorptive capacity or mucosal integrity. Thus, the intestine can still produce loud bowel sounds while its mucosa is eroded and denuded of villi.[51,52] In fact, the use of bowel sounds to drive any clinical decision has never been validated and nowadays guidelines support the use of early enteral nutrition, stating there is no need to wait for bowel sounds.[52,53] Moreover, the presence of bowel sounds poorly reflects postoperative dysmotility as bowel sounds are still audible in the majority of patients with a paralytic ileus. These findings are in line with a recently published prospective study in 124 adult patients undergoing major abdominal surgery. In this blinded observational study, Read et al. found no association between bowel sounds and flatus, bowel movement, or tolerance of oral intake.[54] This further underlines that clinical decisions in intensive care patients with ileus should not be based on auscultatory assessment of bowel sounds.[3,13,45]

Conclusion
The low sensitivity and positive predictive value, together with a poor inter- and intra-observer agreement, demonstrate low accuracy of utilising bowel sounds for clinical decision-making. Thereby, the diagnostic utility of auscultation in differentiating normal from pathological bowel sounds in ICU patients is useless and should be abandoned.

Disclosures
All authors declare no conflicts of interest. No funding or financial support was received.
References

**CASE REPORT**

**Clostridium perfringens: a rare cause of postoperative septic shock**

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Keywords - clostridium perfringens, laparoscopic nephrectomy, septic shock

**Abstract**

Postoperative infections with *Clostridium perfringens* are rare. We report a case of a 59-year-old male, admitted to our ICU for postoperative monitoring after an elective retroperitoneoscopic radical nephrectomy. This patient developed septic shock within 22 hours after laparoscopic surgery. Due to clinical deterioration, he was intubated and taken to the operating room, after a CT scan was performed. Surgery revealed an infected retroperitoneal haematoma, which was drained. Cultures identified *C. perfringens* as the causative pathogen. Postoperative *C. perfringens* infection is potentially life-threatening and rapid antibiotic treatment and surgical drainage play a pivotal role in its management.

**Case report**

Our 59-year-old patient was admitted to our ICU after left-sided retroperitoneoscopic nephrectomy. Surgery was indicated because of suspected renal cell carcinoma. Past medical history of this patient includes: right-sided nephron-urethrectomy due to urothelial cell carcinoma and chronic intermittent haemodialysis, diabetes and morbid obesity. To remove the specimen at the end of the surgical procedure, a lumbotomy was performed. No perioperative antibiotic prophylaxis was given. The surgical procedure was uncomplicated so far and the patient was extubated in the operating room, prior to transfer to the ICU. On admission to the ICU, the only symptoms were local postoperative pain and hypotension (80/40 mmHg). This low blood pressure was within the normal range for this patient and had frequently been reported prior to haemodialysis sessions. Approximately 20 hours after arrival on the ICU, he developed progressive local pain, fever, chills and bruise-like coloration of the skin. The blood pressure dropped further, and the patient became unresponsive. Physical examination revealed subcutaneous emphysema in the left flank. Noradrenaline was started through a central line, empirical antibiotic therapy (piperacillin/tazobactam 4500 mg 3 times daily) was commenced and one dose of gentamycin (6 mg per kg) was administered. Hydrocortisone (100 mg 3 times daily) was added because of the septic shock. Blood cultures were drawn before starting antibiotic therapy. The patient was intubated later that day.

A CT scan (figure 1) was performed and confirmed subcutaneous emphysema in the left flank. Furthermore, free air was seen in the intra-abdominal and left renal fossa space, with some fluid, but no signs of an abscess. The subcutaneous emphysema and intraperitoneal and retroperitoneal air were interpreted as post laparoscopic surgery. After consulting with the urologist,
we chose to manage this patient conservatively. During the following hours, however, further clinical deterioration was noted. Laboratory analysis revealed a CRP of 458 mg/l (144 mg/l, 24 hours earlier) and a lactate of 3.9 mmol/l. The patient was then taken to the operating room (approximately 48 hours after the first surgical intervention) for surgical exploration of the wound. During surgery, an infected deep wound haematoma was found and drained. Intraperitoneal exploration revealed no signs of bowel perforation. The wound was closed leaving two drains and the patient was transferred back to the ICU. During the next 48 hours, the results of cultures (retroperitoneal fluid and tissue, separate cultures) were reported positive for \textit{C. perfringens} (as determined by MALDI-TOF-MS). Repeated blood cultures remained negative. The drains were removed after two days because of no drainage. Piperacillin/tazobactam was continued for six consecutive days. A repeated CT scan revealed fluid in the nephrectomy area, the wound was again surgically drained. A new drain was placed, but fell out spontaneously the day after. From the second operation on, the patient steadily recovered. We started piperacillin/tazobactam per protocol (this is our hospital's protocol in abdominal sepsis without positive cultures). Susceptibility testing revealed \textit{C. perfringens} which was sensitive to piperacillin/tazobactam, so we chose to continue this treatment. Pathology of the renal specimen revealed multiple benign cysts, without signs of carcinoma. Negative pressure wound therapy was started in order to improve wound healing because the past medical history included multiple factors that might restrict wound healing, for example: obesity, diabetes etc. The patient was discharged to the urology ward 11 days after admission to the ICU.

\textbf{Discussion}

Our case illustrates a fulminant septic shock due to a postoperative infection with \textit{C. perfringens}. After \textit{C. perfringens} enters the body (in our case, most likely via the surgical site), the usual manifestation is a necrotising infection of the abdominal wall, often accompanied by hypotension and renal failure due to septic shock. \textit{C. perfringens} consists of five serotypes, A-E. They differ in the types of extracellular toxins they make and their form of tropism. Alpha toxin is a haemolytic toxin which is largely responsible for the tissue necrosis. Under optimal conditions for the bacterium, its multiplying time is as little as eight minutes and is accompanied by gas production. This is the reason why the progression of the infection is so fulminant. Because \textit{C. perfringens} is an anaerobic bacterium, blood supply must be impaired in some way in order for it to thrive. When the ability of the host to mount an inflammatory response involving phagocytes is not suppressed, infection with \textit{C. perfringens} may progress into a fulminant septic shock.

Most cases of gas gangrene arise after penetrating trauma and therefore it is often considered to be a typical military disease: during World War I an estimated 10\% of soldiers lost their lives as a direct result.\cite{8} Postoperative complications account for approximately 30\% of the cases and are most frequently associated with surgery to the appendix, intestine or biliary tract. Known risk factors include: diabetes, coronary artery disease, obesity, malnutrition and intravenous drug use.\cite{5} It seems difficult to determine the incidence of the disease;\cite{7} however, when haemolysis occurs, mortality rates are as high as 70\%.\cite{8} Since \textit{C. perfringens} has the ability to spread very fast, it is of the utmost importance to recognise and treat early. This provides the patient the best chance of recovery.

Harmsen et al.\cite{1} described a case of postoperative infection with \textit{C. perfringens} after laparoscopic cholecystectomy. They report that trocar port infections are rare, only nine cases were reported until 2016. Trocar port wounds are considered ideal sites for infections. A penetrating wound is made, CO\textsubscript{2} is insufflated for creating a pneumoperitoneum. This positive intra-abdominal pressure (12-15 mmHg) and continuous CO\textsubscript{2} flow reduces blood flow in the abdominal wall, making it relatively hypoxic. Trocars damage the abdominal muscles, and cause a ‘chimney effect’\cite{10} (gas passing alongside the trocars, leaving the body), by leakage of CO\textsubscript{2} from the abdominal cavity into the subcutis. This results in subcutaneous emphysema with an environment in which anaerobic bacteria might thrive easily. A trocar infection may have been present in this case.

One of the clinical dilemmas we encountered in this case was to evaluate whether the amount of gas, as visualised by a CT scan, was within the ‘normal range’ for the given time post-laparoscopic surgery. To our knowledge, there are no studies or guidelines elucidating this issue. During retroperitoneoscopic surgery about 3 litres of CO\textsubscript{2} are insufflated in the retroperitoneal space. If there happens to be a tear in the peritoneal membrane, this amount easily doubles.\cite{10} The total amount of CO\textsubscript{2} used during surgery depends on the duration and leakage alongside the trocars. Within 72 hours post-surgery, the CO\textsubscript{2} has usually resolved. Visible intraperitoneal or retroperitoneal gas 72 hours after surgery is considered an ominous finding.
Conclusion
When a patient rapidly develops severe abdominal septic shock following laparoscopic surgery, and subcutaneous emphysema and intra-abdominal air are present, gas gangrene must be considered. These signs should not always easily be attributed to peroperative carbon dioxide insufflation. The treatment of choice for *C. perfringens* infection is surgical debridement of all involved gangrenous tissue, intravenously administered high-dose penicillin, combined with clindamycin\(^1\) and supportive measures. This approach might provide the patient with a better chance for survival.

Acknowledgements
We thank Dr. R.O.A. van Os, radiologist, for providing the scan images.

Disclosures
All authors declare no conflict of interest. No funding or financial support was received.

References
Severe pulmonary involvement in a case of drug reaction with eosinophilia and systemic symptoms (DRESS)

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Keywords - drug reaction with eosinophilia and systemic symptoms (DRESS), shock, acute respiratory distress syndrome (ARDS), intensive care unit, multi-organ failure

Abstract
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, but potentially lethal disorder characterised by fever, exanthema and systemic organ involvement. We present a young woman with a complex medical history, including endocarditis and DRESS, suffering from fever for which antibiotics were prescribed. After initial recovery the fever returned, along with a rash. Her condition progressively deteriorated into shock, requiring ICU admission. Soon after, an acute respiratory distress syndrome (ARDS) evolved, which called for mechanical ventilation with deep sedation and prone positioning. After extensive investigations excluding most autoimmune, infectious and haematological aetiologies, DRESS was considered. Antibiotics were withdrawn and prednisone treatment was started after which the patient eventually recovered.

This case demonstrates the importance for intensivists to recognise DRESS, a potentially life-threatening syndrome, in patients with shock and multi-organ failure, due to its non-infectious process. Awareness is pivotal to discontinuing the causative drugs.

Background
DRESS is the acronym for ‘drug reaction with eosinophilia and systemic symptoms’ and is also known as a drug-induced hypersensitivity syndrome (DIHS).[1] DRESS/ DIHS (further denoted as DRESS) belongs to a family of severe cutaneous drug reactions, together with Stevens-Johnson syndrome, toxic epidermal necrolysis (SJS/TEN) and acute generalised exanthematous pustulosis (AGEP). Symptoms, including fever, enlarged lymph nodes, skin and/or internal organ involvement, mimic various systemic diseases. Exclusion of these other diseases and fulfilling the criteria of the RegiSCAR scoring system (table 1) are essential in the diagnosis of DRESS.[1,2] DRESS is rare: prevalence ranges from 1 case per 1,000 to 10,000 drug exposures. In particular, the burden of DRESS on intensive care admissions is largely unknown. However, it is important that intensivists are aware of this syndrome, as this case will demonstrate.

Case Report
A 35-year-old female presented to the emergency ward of a university hospital with fever, cold chills and tenderness in the right knee joint for three days. Almost a year before, she was admitted for four months because of pneumococcal pneumonia complicated by aortic valve endocarditis for which an aortic valve replacement had been performed. This episode was furthermore complicated by septic emboli to the brain and thoracic vertebrae and an aortic root abscess for which a Bentall procedure was needed. She received long-term antibiotic therapy. During that admission she had a drug reaction with eosinophilia and systemic symptoms for which she was successfully treated with prednisone. She was prescribed piperacillin/tazobactam, benzylpenicillin, ceftriaxone, vancomycin, diclofenac and tramadol, but careful evaluation at the allergology department could not reveal the culprit agent. Finally, she recovered completely.

At the current admission, her vital signs were normal except for a low-grade fever (38.0°C) and local knee joint swelling with tenderness. Her medication was limited to acenocoumarol and acetaminophen. Empirical therapy with teicoplanin and moxifloxacin was started, aimed to cover a possible bacterial endocarditis, graft infection or arthritis (see figure 1A for an overview of antibiotic use). Knee arthrocentesis resulted in a dry tap and ultrasound of the knee was normal. Soon after admission she developed gastrointestinal symptoms, attributed to moxifloxacin which was therefore switched to ciprofloxacin. Early after administration of intravenous ciprofloxacin, however, a subtle but pruritic skin rash with a papular erythematos
Severe pulmonary involvement with DRESS aspect developed. Quinolones were stopped and teicoplanin was continued. Blood cultures were repetitively negative as were further investigations including cardiac ultrasound, and MRI of the knee, heart and aortic graft. An infection was thus considered unlikely and the antibiotics were stopped after six days. The skin eruptions had improved and the fever had resolved. However, nine days after admission, there was a sudden recurrence of fever, an increase in C-reactive protein, mild eosinophilia of 590 cells per µl and atypical lymphocytes on the blood smear. Meropenem was prescribed targeting a possible vascular graft infection or endocarditis, which would have been insufficiently treated in the earlier prescribed antibiotic regimen. However, the fever persisted and a few days later a new skin rash appeared with generalised erythematous eruptions on her back, torso and extremities. To cover the more resistant Gram-positive species as well, teicoplanin was added to the antibiotic regimen. At day 14 her condition, however, worsened with haemodynamic instability and respiratory distress for which she was transferred to the ICU and immediately intubated. Consistent with ARDS, severe hypoxaemia was present with a PaO2/FiO2 ratio declining under 100 mmHg, in association with the development of bilateral infiltrates (figure 1B) and normal cardiac function on echocardiography. With further respiratory deterioration, neuromuscular blockade and prone positioning was required after lung protective mechanical ventilation was set up. Concomitantly there was evidence of liver and kidney involvement with respectively elevated serum transaminases and creatinine, although the latter developed after ICU admission and could just as well be secondary to the patient’s state of shock.

Our differential diagnosis was broad and included ARDS due to recurrent endocarditis with septic pulmonary involvement, a pulmonary infection or a haematological or autoimmune disease. PET-CT scan showed bilateral pulmonary opacities and widespread lymphadenopathy, but no signs of graft infection (figure 1B). Pathological examination of bone marrow and lymph node ruled out haemophagocytic lymphohistiocytosis and lymphoma. Cultures and microbial testing of blood and bronchoalveolar lavage, including a viral panel, Pneumocystis jiroveci and Aspergillus were negative. In addition, no herpes viruses were detected and autoimmune serology was also negative, making an autoimmune disease unlikely. Because of the continuing deterioration under antibiotic treatment DRESS was considered and rated as a ‘definite case’ in compliance with the RegiSCAR criteria (table 1) as a diagnosis by exclusion.[1,2] All antibiotics were discontinued and prednisone treatment was started at 1 mg/kg, resulting in a gradual recovery. Extubation followed after 12 days of mechanical ventilation and eventually our patient was discharged to a rehabilitation clinic with a tapering prednisone regimen. Six months after the initial presentation she returned home. Follow-up in the outpatient clinic again included evaluation of the possible culprit drug which was thought to be teicoplanin. However, she received a relative contraindication for beta-lactam antibiotics in the future as well.

Discussion
We present a young woman who was admitted to the ICU with multi-organ failure and severe ARDS as manifestations of DRESS. This diagnosis was supported by negative test results for infectious, haematological or autoimmune disease in combination with the ‘definite’ categorisation according to the RegiSCAR criteria (table 1). In addition, her gradual recovery after withdrawal of all antibiotics and initiation of prednisone
therapy favoured the diagnosis of DRESS. This is one of the few reports linking DRESS with ARDS (search on Medline and PubMed with search criteria “DRESS”, “drug reaction with eosinophilia and systemic symptoms,” “DIHS,” “drug-induced hypersensitivity syndrome,” “drug induced ARDS,” “drug pulmonary involvement,” “drug hypersensitivity lung” and “drug hypersensitivity pulmonary”).

Awareness is critical as DRESS is potentially life threatening but, as this case demonstrates, it may often go unrecognised for several reasons: symptoms are non-specific, it is a diagnosis by exclusion requiring expert-based criteria and the time of dosage to symptoms may vary greatly.[11] Symptoms may occur 2-6 weeks after prescription of the culprit drug, or in hours to days in case of a rechallenge.[12] Based on the temporal relationship between the onset of symptoms and the initiation of the drug (figure 1A), the glycopeptide and quinolone antibiotics could have been the culprit drug. Quinolone antibiotics, however, have not been reported to cause DRESS,[11] although they have been implicated in SJS/TEN and AGEP.[2]

It is thus reasonable to specify only teicoplanin as the culprit agent. DRESS due to a combination of vancomycin and teicoplanin has recently been described by Miyazu et al.[3] The possibility of the patient’s initial presentation being a relapse of the previous episode of DRESS a year before was considered, but could not be proven since the criteria (table 1) were not met at that time. In the last eight months there had been no other drug exposure, including possible over-the-counter drugs, than acenocoumarol and acetaminophen making the initial phase as a prodromal stage of DRESS unlikely as well. However amoxicillin-induced flares have been reported, implying a relative contraindication for beta-lactam antibiotics in patients with DRESS.[4]

In general, severe cutaneous drug reactions are elicited by excessive or inappropriate activation of an immune response, due to the binding of foreign antigens (i.e. the drug) to T-cell receptors.[5] This leads to a dramatic expansion of functional T-lymphocytes and the appearance of autoantibodies to various epidermal proteins. This drug-specific T-cell proliferation may have an important role in the known association with reactivation of latent human herpesvirus (HHV) 6, and to lesser extent with HHV7, Epstein-Barr virus and Cytomegalovirus reactivation.[1,3,5,6]

Pulmonary involvement in drug reactions is well known and characterised by pulmonary oedema and interstitial lung disease, and rarely with a severe presentation consistent with ARDS at the extremity of the spectrum of pulmonary involvement.[7,8] Data regarding the course and outcome of patients with severe DRESS admitted to the ICU are limited to one retrospective study in 23 French ICUs.[9] The researchers identified 21 patients with a probable or definite diagnosis of DRESS in ten years’ time (based on the RegiSCAR score, table 1). All had fever and erythematous exanthema (part of database search criteria);

<table>
<thead>
<tr>
<th>Table 1. The RegiSCAR group diagnosis score for drug reaction with eosinophilia and systemic symptoms (DRESS)[1,2]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever (≥38.5°C)</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td><strong>Atypical lymphocytes</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td><strong>Eosinophilia</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td><strong>Internal organ involvement</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td><strong>Resolution in &gt;15 days</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>≤1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
</tbody>
</table>

A schematic scoring system to grade the possibility of DRESS: <2 no case; 2-3 possible case; 4-5 probable case; > 5 definite case.[2,3] The last column represents the scoring for our patient, 6 points in total

a Generalised lymphadenopathy on computed tomography (CT), see also figure 1
b Biopsy of the skin was not performed
c Including pulmonary, hepatic and possibly renal involvement, although this could also be secondary to shock

d More than half were associated with shock (15/21), acute renal failure (18/21), mechanical ventilation (13/21; no information about ARDS diagnosis in this population) and acute hepatitis (11/21). The disease severity of this highly restricted population selection is further demonstrated by a mortality rate of almost 50%. [9]

DRESS is rare, but the low incidence may be explained by underreporting or unawareness of the syndrome with diagnostic hallmarks such as fever, eosinophilia, generalised rash with typical mucosal involvement, and multi-organ involvement. Nevertheless, the high mortality compatible with severe shock and multi-organ failure emphasises the importance for intensive care physicians to consider DRESS in their differential diagnosis. This is imperative, as early recognition with prompt withdrawal of the culprit drug to stop the harmful exposure is considered the key treatment. In addition, corticosteroids are advised, but future studies are needed to explore their role in the treatment of DRESS.[1]

Conclusion

This case demonstrates that intensive care physicians should include DRESS in their differential diagnosis of ARDS in patients with a distributive shock accompanied by systemic symptoms without evidence of definite aetiology. This is important as it has treatment implications, namely the withdrawal of the possible causative agent. Thus earlier recognition implies shorter exposure. It is possible that this could have led to a shortened period of mechanical ventilation and haemodynamic

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Ce geneesmiddel onderworpen aan sommige Monitoring

NAAM VAN HET GENESMIDDEl: CRESEMBA 200 mg poeder voor concentraat voor oplossing voor infusie

Pièces: ECHER CRESEMBA 200 mg poeder voor concentraat voor oplossing voor infusie of CRESEMBA 100 mg harde capsules.

Informatie over de geneesmiddel en het gebruik van CRESEMBA 200 mg poeder voor concentraat voor oplossing voor infusie


3. Miyaizu D, Kodama N, Yamashita D, et al. DRESS syndrome caused by cross-


Mortaliteit vanaf de eerste dosis tot aan dag 84 was niet verschilend tussen isavuconazol en voriconazol, in zowel de ITT-populatie (-1,1% [95% BI: -8,9%-6,7%]) als de mITT-populatie (-5,5% [95% BI: -16,1–5,1]).

De meeste patiënten (84%) hadden als onderliggende aandoening een hematologische maligniteit. De gemodificeerde ITT-populatie en mITT-populatie waren schilrend tussen isavuconazol en voriconazol, in zowel de ITT-populatie (-1,1% [95% BI: -8,9%-6,7%]) als de mITT-populatie (-5,5% [95% BI: -16,1–5,1]).

Resultaten

Tabel 1. Doseringsschema isavuconazol en voriconazol.

<table>
<thead>
<tr>
<th></th>
<th>Voorbeelddosering isavuconazol</th>
<th>Voriconazol voorbeelddosering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groep</td>
<td>Dag 1</td>
<td>Dag 2</td>
</tr>
<tr>
<td></td>
<td>Vanaf dag 3</td>
<td>Vanaf dag 3</td>
</tr>
<tr>
<td></td>
<td>200 mg intraveneus per dag</td>
<td>4 mg/kg intraveneus per dag</td>
</tr>
<tr>
<td></td>
<td>of 200 mg oraal per dag</td>
<td></td>
</tr>
</tbody>
</table>

Strijd tegen infecties

Waarom is isavuconazol een goed alternatief?

Isavuconazol geeft minder medicatie gerelateerde bijwerkingen, zoals bijwerkingen van de lever. Er was ook geen verschil in overleving op dag 84 van beide behandelingen: 57% bij isavuconazol versus 50% bij amfotericine B (HR 0,831 [95% Cl: 0,367–1,882]; p=0,653).

Isavuconazol is geschikt om bij patiënten met nierinsufficiëntie te worden gebruikt. Het biedt een alternatief voor patiënten die vanwege een hoge toxiciteit van voriconazol niet meer worden behandeld met dit medicijn. Isavuconazol is ook een optie bij aspergillose en zygomycose.
CASE REPORT

Small bowel obstruction after laparoscopic Roux-en-Y gastric bypass presenting as acute pancreatitis: a case report

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Department of 1Intensive Care, 2Gastroenterology and Hepatology, and 3Surgery, Sint Anna Hospital, Geldrop, the Netherlands.

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Keywords - Roux-en-Y, gastric bypass, pancreatitis, pancreatic enzymes, small bowel obstruction, biliopancreatic limb obstruction.

Abstract
Small bowel obstruction is a common and potentially life-threatening complication after laparoscopic Roux-en-Y gastric bypass surgery. We describe a 30-year-old woman who previously underwent gastric bypass surgery. She was admitted to the emergency department with epigastric pain and elevated serum lipase levels. Conservative treatment was started for acute pancreatitis, but she showed rapid clinical deterioration due to uncontrollable pain and frequent excessive vomiting. An abdominal computed tomography scan revealed small bowel obstruction and surgeons performed an exploratory laparotomy with adhesiolysis. Our patient quickly improved after surgery and could be discharged home. This case report emphasises that in post-bypass patients with elevated pancreatic enzymes, small bowel obstruction should be considered and early computed tomography scan is required in these patients.

Introduction
Laparoscopic gastric bypass surgery is the most commonly performed bariatric procedure worldwide. In the Netherlands alone, approximately 8,139 gastric bypass operations are performed annually. Laparoscopic Roux-en-Y gastric bypass (LRYGB) is considered the gold standard for the treatment of severe obesity in patients with a body mass index (BMI) ≥40 kg/m² or ≥35 kg/m² with obesity-related comorbidity. General surgeons, emergency physicians and other clinicians will more frequently encounter postoperative LRYGB complications because of the increasing number of patients undergoing bariatric surgery. Small bowel obstruction is described as a common complication after LRYGB surgery and has an incidence of 1.27-5%. The obstruction can be difficult to diagnose due to the changed anatomy of the gastrointestinal tract and symptoms may vary. During LRYGB, the upper part of the stomach is stapled to form a small pouch and is connected to the jejunum, bypassing the remnant stomach, duodenum, bile ducts and a proximal part of the jejunum (figure 1). This bypassed part forms the biliopancreatic limb, which delivers bile and pancreatic enzymes to the common intestinal channel. Physicians should have a thorough knowledge of post-bypass anatomy and should be extra attentive to suspecting small bowel obstruction within this population, because misdiagnosis can have disastrous outcomes. In this report we describe the difficulty of diagnosing small bowel obstruction in post-LRYGB patients and why elevated pancreatic enzymes can indicate an obstruction in these patients. The purpose of this manuscript is to emphasise that in post-bypass patients with abdominal pain and elevated pancreatic enzymes, small bowel obstruction should be considered and that this condition requires rapid diagnosis using computed tomography. Contrary to other conditions, such as acute pancreatitis, surgical intervention is needed in most cases.

Case report
A 30-year-old woman was referred by a general practitioner to our emergency department (ED) with complaints of continuous epigastric pain, despite 10 mg of morphine intramuscularly one hour prior to presentation. Her medical history revealed that she had undergone more than 15 abdominal operations, including gastric band placement (2011), laparoscopic Roux-en-Y gastric bypass (2013), laparoscopic cholecystectomy (2017) and laparotomic adhesiolysis due to obstruction of the biliopancreatic limb (2017). In the ED we saw a woman in severe pain, with nausea and vomiting. Her last bowel movement was that day and her vital signs were normal. Physical examination revealed a soft abdomen with normal bowel sounds, but maximal abdominal tenderness in the epigastric region and rebound tenderness. Laboratory tests revealed hyperlipasaemia with hyperamylasuria and a minor elevation of liver function tests (table 1). Unfortunately, serum amylase levels were not measured. Abdominal radiography showed mildly dilated small bowel loops with some air-
fluid levels. An abdominal ultrasound did not expose gallstones or dilated intrahepatic or extrahepatic bile ducts. The pancreas could not be visualised due to intestinal gas, but slightly dilated bowel loops were seen with normal peristalsis. We considered that our patient was suffering from acute pancreatitis. She did not use alcohol or eliciting drugs, had not recently undergone an endoscopic retrograde cholangiopancreatography and her calcium and triglyceride levels were normal. Therefore, the cause of the pancreatitis could be gallstones that were not visualised on ultrasound. She was admitted to the ward with conservative treatment: nil by mouth, intravenous fluids, pantoprazole, antiemetics and analgesics. The patient refused a nasogastric tube due to unpleasant experiences with previous tubes. On the ward, our patient had uncontrollable abdominal pain, despite paracetamol, diclofenac and pethidine. She had severe persistent vomiting and on physical examination her abdomen was rigid and bowel sounds were absent. The patient was transferred to the intensive care unit (ICU) because of this clinical deterioration, where she received morphine intravenously. At the ICU, her laboratory tests revealed progressively elevated liver function tests (table 1), suggesting that acute biliary pancreatitis might still be the cause of our patient’s symptoms. However, the severity of pain, the excessive vomiting and the new findings on physical examination did not match this diagnosis. At this point we considered a torsion or obstruction of the biliopancreatic limb. An abdominal computed tomography scan was ordered and showed dilated small bowel loops with a change in calibre and collapsed loops in the pelvic area (figure 2), suggesting small bowel obstruction. No signs of pancreatitis were observed. The patient required surgical treatment that same day. Surgeons performed an exploratory laparotomy with adhesiolysis 50 cm distal to the jejunojejunostomy. The patient quickly showed clinical improvement after surgery; she was no longer vomiting and her pain diminished. Also, her lipase level and liver function tests returned to normal (table 1). The patient could be transferred to the surgical ward and was discharged home on postoperative day 4.

Discussion

We present a case of a young woman with a history of Roux-en-Y gastric bypass surgery, who presented with epigastric pain, vomiting, hyperlipasaemia and elevated liver function tests. These findings were misinterpreted as acute biliary pancreatitis and the patient was treated conservatively, as is required in acute pancreatitis. However, after clinical deterioration, computed tomography revealed small bowel obstruction without any signs of pancreatitis. The patient underwent an exploratory laparotomy with adhesiolysis, after which she rapidly improved and could be discharged home on postoperative day 4.

Small bowel obstruction after Roux-en-Y gastric bypass

Small bowel obstruction after LRYGB can be difficult to diagnose. The most common symptoms include abdominal pain, nausea and vomiting. Our patient vomited upon admission and progressed to excessive vomiting on the ward despite antiemetics. A variety in the expression of symptoms is described among post-bypass patients. Vomiting is reported as retching or small amounts of clear emesis, due to the small stomach pouch. Bilious vomiting indicates an obstruction at or below the site of the jejunojejunostomy. However, vomiting might also be absent when the obstruction only involves the biliopancreatic limb. This illustrates the difficulty in recognising symptoms of small bowel obstruction in post-bypass patients and why attending physicians should have knowledge of the post-bypass anatomy.

The diagnosis can also be challenging because of the low sensitivity of radiological studies in post-LRYGB patients. The abdominal radiograph of our patient did show some signs of small bowel obstruction, but the computed tomography scan diagnosed the adhesive obstruction. This corresponds with a study which found a sensitivity of 33.3% for plain abdominal radiography to diagnose small bowel obstructions in the post-LRYGB population, compared with a sensitivity of 70-80% in the general population. This study also found a sensitivity of 51.1% for computed tomography scans to diagnose obstruction in the post-LRYGB population, compared with 80-90% in the general population. This means that negative radiological studies do not rule out small bowel obstruction in the post-bypass population. Therefore, in this case where abdominal radiography did not explain the symptoms, a computed tomography scan should have been performed immediately. In case of negative radiological studies, a strong clinical suspicion is leading in decisions to perform laparoscopic exploration and should be done without delay.

Our patient developed small bowel obstruction four years after her LRYGB, caused by adhesions that obstructed the common intestinal channel. The reported interval between LRYGB surgery

Table 1. Laboratory results

<table>
<thead>
<tr>
<th></th>
<th>t0</th>
<th>t1</th>
<th>t2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>7.3 mmol/l</td>
<td>6.8 mmol/l</td>
<td>6.4 mmol/l</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>14.4 x10^9/l</td>
<td>6.4 x10^9/l</td>
<td>7.5 x10^9/l</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>264 x10^3/l</td>
<td>234 x10^3/l</td>
<td>258 x10^3/l</td>
</tr>
<tr>
<td>Sodium</td>
<td>141 mmol/l</td>
<td>139 mmol/l</td>
<td>140 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6 mmol/l</td>
<td>3.6 mmol/l</td>
<td>3.6 mmol/l</td>
</tr>
<tr>
<td>Urea</td>
<td>3.0 mmol/l</td>
<td>3.9 mmol/l</td>
<td>3.9 mmol/l</td>
</tr>
<tr>
<td>Creatinine</td>
<td>65 µmol/l</td>
<td>47 µmol/l</td>
<td>60 µmol/l</td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;90 ml/min</td>
<td>&gt;90 ml/min</td>
<td>&gt;90 ml/min</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.41 mmol/l</td>
<td>2.30 mmol/l</td>
<td>2.30 mmol/l</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>14.5 µmol/l</td>
<td>69.3 µmol/l</td>
<td>69.3 µmol/l</td>
</tr>
<tr>
<td>Bilirubin (conjugated)</td>
<td>82 %</td>
<td>69.3 %</td>
<td>69.3 %</td>
</tr>
<tr>
<td>AST</td>
<td>89 U/l</td>
<td>701 U/l</td>
<td>192 U/l</td>
</tr>
<tr>
<td>ALT</td>
<td>39 U/l</td>
<td>473 U/l</td>
<td>338 U/l</td>
</tr>
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<td>Urine amylase</td>
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and surgical intervention for small bowel obstruction varies between 1 to 1,215 days after surgery, but seven years is also mentioned.[1,3] Our patient developed the obstruction quite late. However, she had already undergone adhesiolysis due to an obstruction earlier that year. This case also corresponds with studies stating that early small bowel obstructions mainly result from technical problems with the anastomosis, whereas late obstructions tend to affect the common channel and generally originate from internal herniation or adhesions.[64] Adhesions cause 13.7-27.5% of all obstructions.[1,4-6,8] Small bowel obstruction should have been suspected earlier, because of the patient’s medical history of adhesions.

Elevated pancreatic enzymes as an indicator of small bowel obstruction after Roux-en-Y gastric bypass

An association between small bowel obstruction after LRYGB and elevated amylase or lipase levels has been reported before.[4,7] The lipase level in our patient was 8,600 IU/l with elevated amylase urine levels and slightly elevated liver function tests. This mislead us in diagnosing acute (biliary) pancreatitis in our patient. One study measured elevated serum amylase and/or lipase levels in 48% of small bowel obstructions after LRYGB. In 28.6% of patients both enzymes were elevated, whilst some patients only had amylase (46.4%) or lipase (25%) elevation. The range of amylase levels in this study was between 127-328 IU/l (mean 152.1) and lipase levels between 53-148 IU/l (mean 87.9), which is lower compared with the levels in acute pancreatitis.[7] The same study concludes that elevated pancreatic enzymes have a high sensitivity for detecting acute small bowel obstructions (64%), especially in the biliopancreatic limb (94%).[7] Although our patient had an acute obstruction of the common intestinal channel, the elevated lipase level should have suggested small bowel obstruction.

In small bowel obstructions, elevated pancreatic enzymes result from the inability of the pancreas to secrete its enzymes against the increased intraluminal pressure in the duodenum. The same aetiology exists for intraluminal pressure in the duodenum. The same aetiology exists for elevated liver function tests.[85,86] In this case, the extremely high level of lipase could imply some inflammation of the pancreas due to stasis of pancreatic enzymes, despite the normal aspect of the pancreas on computed tomography. Thereby, elevation of these markers in post-bypass patients may be misleading and can indicate an obstruction of the biliopancreatic limb or distal to the jejunojunostomy.[8]

Misdiagnosis of small bowel obstruction as acute pancreatitis can have disastrous consequences because of the non-surgical management, whilst the obstruction can rapidly worsen to bowel ischaemia, perforation and even death.[85,87] Guidelines for acute pancreatitis recommend a computed tomography scan when there is diagnostic uncertainty, when clinical findings suggest severe acute pancreatitis, when there is no response to conservative treatment or in case of clinical deterioration. The initial scan should be performed at least 72-96 hours after the onset of symptoms, because necrosis may not yet be visible and early imaging does not affect the management or prognosis.[8] In post-bypass patients with elevated pancreatic enzymes, computed tomography should be performed early due to diagnostic uncertainty and the possible life-threatening complications of small bowel obstruction that require direct operative management.

Conclusion

An increasing number of patients undergo laparoscopic Roux-en-Y gastric bypass, so complications will be seen more frequently at the emergency department and intensive care unit. A well-known complication is small bowel obstruction. This can be difficult to diagnose, due to the altered gastrointestinal anatomy that gives a variety of symptoms and a lower sensitivity of radiological studies. Misdiagnosis of small bowel obstruction as acute pancreatitis can be catastrophic due to the non-surgical management. Elevated pancreatic enzymes can indicate small bowel obstruction in post-LRYGB patients and a computed tomography scan early in the course of the illness is mandatory in these patients because of diagnostic uncertainty and possible bowel ischaemia or perforation. In case of negative laboratory or radiological results, high clinical suspicion should be leading in the decision for surgical exploration.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

References


Figure 2. Computed tomography scan, made in a lateral position due to vomiting and risk of aspiration, demonstrating a small bowel obstruction in the patient.
The NVIC will award a prize for the best Review and the best Original Article in 2018. In both categories the top 3 papers in 2018 will be nominated by the executive board of the Netherlands Journal of Critical Care. NVIC members may vote and the prizes will be awarded during the Intensivistendagen in February 2019.

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The great imitator, imitated

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Keywords - tuberculosis, miliary, hydrocephalus, carcinoma

Case
A 72-year-old female, born in Surinam, presented to the emergency unit of a general hospital after a month of non-productive coughing and a week of being unwell. Except for increasing chronic lower back pain, she had no other complaints and there was no fever. She had no history of tobacco use and her medical history was unremarkable other than insulin-dependent diabetes and dyslipidaemia. A chest X-ray showed uniformly distributed miliary deposits (commonly defined as: innumerable, uniformly distributed, 1-4 mm pulmonary nodules) and consolidation in the left lower lobe (figure 1).

With the hypothesis of miliary tuberculosis, the patient was admitted to the pulmonology ward. A bronchoscopy showed no endobronchial abnormalities and a bronchoalveolar lavage was performed in the right upper lobe. Both the auramine-rhodamine stain and the Ziehl-Neelsen stain turned out positive, after which treatment with tuberculostatic drugs (isoniazid 300 mg/day, rifampicin 600 mg/day, ethambutol 1000 mg/day and pyrazinamide 1500 mg/day) was initiated and a PCR on Mycobacterium tuberculosis was ordered. The PCR later turned out to be negative. A PCR on non-tuberculous mycobacteria was not performed. The HIV test was negative.

After two days of treatment, the patient’s consciousness deteriorated. A CT and MRI scan of the brain showed hydrocephalus with dilated lateral and third ventricles, a normal aqueduct and fourth ventricle and extensive leukoaraiosis. This was interpreted as impaired resorption of cerebrospinal fluid due to tuberculous meningitis.

Because of progressively deteriorating consciousness and nuchal rigidity, dexamethasone was started and the patient was transferred to our centre for placement of an external ventricular drain.

After the transfer, a previously obtained interferon-gamma release assay (IGRA, QuantiFERON) test turned out negative which, even though there are many cases of active tuberculosis with a negative IGRA, initiated doubt about the diagnosis of tuberculosis. Repeated cerebrospinal fluid samples showed no leucocytosis or low glucose and the auramine-rhodamine stains and PCR on Mycobacterium tuberculosis was negative.

Figure 1. Chest X-ray.

False-positive results from both the auramine and Ziehl-Neelsen stains are rare. This can result from technical errors during the staining process, such as the re-use of containers or positive slides, contamination of the stain by using water containing environmental mycobacteria, use of scratched slides, inadequate decolourisation, etc. We consulted the microbiologist of the referring hospital about the discrepancies in the results and learned that the initial auramine-rhodamine...
and Ziehl-Neelsen stains were only doubtfully positive and that a second stain on a new glass had turned out negative. After insertion of the external ventricular drain her consciousness improved. A CT scan of the lungs was performed, confirming the miliary deposits previously suggested on the chest X-ray (figure 2), a pulmonary embolism in the left lower lobe segmental artery, consolidation in the left lower lobe being interpreted as pulmonary infarction (figure 3) and no significant mediastinal lymphadenopathy. A bronchoscopy was repeated to obtain transbronchial biopsies from the left lower lobe. Unfortunately, 24 hours later our patient needed to be intubated because of respiratory insufficiency. The results of the transbronchial biopsies showed an adenocarcinoma of which the immunohistochemical profile fitted a primary lung malignancy.

The cytology of the cerebrospinal fluid showed atypical cells, which in this context were most likely a metastasis of an adenocarcinoma. Together these results took us to the final diagnosis of a primary lung carcinoma with diffuse miliary pulmonary and leptomeningeal metastasis. Neurologically the patient did not improve, she was localising to pain, but not obeying commands and was therefore maintained on mechanical ventilation. Together with the neurologist and the pulmonologist, we concluded that the prognosis was grave and life support, including mechanical ventilation, was terminated, after which our patient died. Autopsy was not performed.

All cultures from the bronchoalveolar lavage, cerebrospinal fluids and the pulmonary biopsy turned out negative for mycobacteria.

Conclusion
In conclusion, we present a patient with miliary pulmonary abnormalities suspect of tuberculosis. Tuberculosis is known as the ‘great imitator’ since the disease may mimic a variety of other diseases. In this case, however, the great imitator was imitated itself since the patient was diagnosed with pulmonary adenocarcinoma, with miliary pulmonary metastases and leptomeningeal metastasis. While the primary thought is often tuberculosis when confronted with miliary pulmonary abnormalities, it is important to realise that there is quite an extensive differential diagnosis. The differential diagnosis of a miliary pattern on a chest X-ray in an afebrile patient is: tuberculosis, fungal infection, viral infection (such as varicella pneumonia), sarcoidosis, silicosis, haemosiderosis, hypersensitivity pneumonitis, (eosinophilic) granulomatosis with polyangiitis ((e)GPA), eosinophilic pneumonia, pulmonary alveolar proteinosis, Langerhans cell histiocytosis and miliary metastasis of cancer (melanoma, sarcoma, carcinoma). As always, we need to keep an open mind and realise the importance of pulmonary biopsy.

Disclosures
The author declares no conflict of interest. No funding or financial support was received.
Several breakthroughs in medicine, such as the discovery of penicillin, have been the merit of a single individual. Those days are over and will not return, as current medical research is more than ever a team effort. Multiple disciplines are involved due to the complexity of the studied topics and the need to use advanced research methodology that comes with very specific expertise. This holds particularly true for intensive care medicine, with heterogeneous patient populations, time-dependent determinants and outcomes, and numerous confounders. As patient-centred outcomes in intensive care medicine usually have a multifactorial aetiology, clinical studies in this field must be large enough to demonstrate meaningful effects. Large multicentre investigations are therefore needed, both for inclusion of a sufficient number of patients and for high-level scientific input. To achieve this, collaboration is essential. However, multicentre studies are costly, to a large extent due to legal regulations that have become more and more complex. Obviously, this poses a challenge on how to optimise resources for medical research. This does not imply it is time to cut down on research efforts in our field. On the contrary, it calls for organisation of our efforts to improve the quality of intensive care medicine and to be able to compete with other medical specialties for the limited research funding. Intensive care is at the heart of modern medicine. Without intensive care units (ICUs), high-risk therapies such as cardiac surgery or trauma surgery would take their death toll. The increase in demand for ICU facilities further underlines that modern intensive care is indispensable in modern medicine. However, fundamental issues in intensive care medicine are currently unresolved. For many routine treatments, it is currently unclear whether these are effective. New tools for diagnosis and management raise new questions, and emerging therapies need to be tested. Other medical disciplines and intensive care medicine abroad have shown how much can be gained with collaboration. Examples of successful research collaborations from other disciplines in the Netherlands and from intensive care medicine abroad

Several medical disciplines have been very successful in establishing research consortia in the Netherlands, such as the Dutch Pancreatitis Study Group and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON). The resulting synergy of research-based patient care and clinical research have led to impressive breakthroughs. These have boosted quality of care and research, and have also given rise to opportunities to acquire new research funding. Examples can also be found in intensive care medicine, as shown by the Australian and New Zealand Intensive Care Society (ANZICS), Canadian Critical Care Trials Group (CCCTG) and the Scandinavian Critical Care Trials Group (SCCTG).

In the Netherlands, several important investigator-initiated multicentre studies have been performed in intensive care medicine. However, these efforts were isolated and lacked long-term organisation and structural funding.

Aims of a collaborative research network

To improve research opportunities in the Netherlands, the Research Collaboration Critical Care in the Netherlands (RCCCNet) has recently been founded. The overall aim of RCCCNet is to improve opportunities for research in the field of intensive care medicine in the Netherlands. The first objective is to facilitate collaboration between participating ICUs in our country. We aim to create a network of ICUs from both academic and non-academic hospitals, as well as researchers active in intensive care medicine, related fields and/or research methodology. Infrastructure and expertise that has grown locally can thus be shared within the network to facilitate future collaborative efforts. This not only refers to research methodology, but also to knowhow regarding complex regulations, and the process of obtaining research funding. The second aim is to increase the financial means to execute...
these investigations. We realise that it is challenging to get a ‘bigger part of the cake’ as current research budgets are under pressure. Compared with many other fields of medical research (such as oncology, cardiovascular medicine and dementia) intensive care medicine has significantly less resources for research. There are no funds solely dedicated to intensive care medicine and intensivists are usually not in key positions in general funding agencies where scientists from all disciplines compete for a limited number of grants.

To increase resources, we need to bring together organisations that are relevant for research in intensive care medicine. These include the Dutch Society of Intensive Care (NVIC), public parties (The Netherlands Organisation for Health Research and Development, ZonMW; Netherlands Organisation for Scientific Research, NWO) and industry (pharmaceutical companies and manufacturers of devices used in the ICU). Public and private parties are part of society, and at present society may not be sufficiently aware of what intensive care medicine entails, nor what its relevance is in modern medicine. We therefore need to reach out to the public to improve awareness of intensive care medicine. Important in this regard is that intensive care medicine is very expensive and that cost-effectiveness has great societal impact. As fundamental issues in intensive care medicine are currently unresolved, research should not, however, be limited to health economic studies alone.

We envision that in the near future, two or three large-scale, non-commercial multicentre studies could be running simultaneously, with participation of a large number of Dutch ICUs. These studies could be interventional randomised clinical trials, but also observational investigations. In selected centres, sub-studies could be performed on separate outcomes. In addition, we wish to enhance collaboration in critical care translational research. We envision that the already high standard of translational research can be further improved by exchanging ideas and collaborative investment in expensive, highly-specialised laboratories, equipment and personnel.

Our aims to facilitate collaboration and to increase financial means are closely connected. A research network with a high-level infrastructure, expertise and knowhow will be extremely helpful in obtaining new funding for future investigations. An active research network will further mature Dutch intensive care medicine, and improve visibility towards fundraisers and society. On the other hand, any increase in financial means for research will strongly stimulate collaboration and ultimately clinical care.

Organisational structure
To achieve these goals, an executive committee has been established. To be effective and decisive, the executive committee will have a limited number of members to lead RCCCNet and to coordinate the efforts of the steering committee.

The steering committee will consist of representatives from participating ICUs from academic and non-academic hospitals, scientists from related fields such as intensive care epidemiology or sepsis biology, as well as representatives of former patients such as Family and Patient Centred Intensive Care (FCIC). All RCCCNet members will have the opportunity to contribute to the research agenda, as described below. In addition, steering committee members will be able to give input to new study proposals and become principle investigators, trial coordinators, members of a Data Safety Monitoring Board, or contributing investigators by enrolling patients for a certain study. Membership of the steering committee provides the opportunity to be involved in large and relevant trials and to publish in top-ranked journals. Importantly, credits such as authorship of resulting publications, will be shared among everyone who has made a substantial contribution.

RCCCNet has been endorsed by the NVIC board and will regularly report to the NVIC members. A formal statement will be put in the statutes to ensure scientific independence of RCCCNet. NVIC will provide administrative support.

The research agenda
A broadly supported research agenda may help to keep the focus on the topics that are considered most urgent by the research community. In contrast to other medical disciplines, there is currently no research agenda on intensive care medicine in the Netherlands. This is unfortunate, as important funding agencies such as ZonMW may have a preference for research proposals of topics that are listed on the research agenda of the involved medical discipline.

We envision that all RCCCNet members will have the opportunity to contribute to the development of a research agenda for intensive care medicine. We propose that members choose a subfield of their interest and make a short list of topics with a high priority for investigation. It is encouraged to focus new grant proposals on one of these topics. When a grant proposal is finalised, it will be distributed among all steering group members for input and feedback to improve the chances of a successful competitive bid to a funding agency. If the proposal is granted, representatives of each centre can decide whether or not to participate in this specific investigation.

Importantly, it is envisioned that the consortium is not meant to act as a ‘trial bureau’, only to facilitate the conduct of randomised clinical trials. RCCCNet aims to facilitate interaction between investigators, to provide a platform for new and clinically relevant research ideas, and eventually to improve the chances of successful applications to funding agencies. In addition, RCCCNet aims to facilitate the conduct of studies. Commitment, investment of time and financial resources will be needed.
Kick-off

On the 21 September 2018, a meeting will be organised to which all intensive care physicians and researchers interested in this collaboration effort are invited. An invitation will also be sent by email, with the exact location. We hope to be able to welcome you all in order to start mapping relevant research topics. Now is the time to improve research collaboration in critical care in the Netherlands.

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References
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| **NVIC Basiscursus echografie** | Monday 10 September - Tuesday 11 September 2018  
Tuesday 30 October - Wednesday 31 October 2018  
Monday 3 December - Tuesday 4 December 2018 | **ESICM LIVES 2018** | Paris 20-24 October 2018 |
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- conclusions are presented in a clear and concise manner and are supported by the data;
- the research meets all applicable ethical standards;
- the article adheres to appropriate reporting guidelines and community standards for data and data disclosure;
- when reporting the results of a randomised controlled trial, author(s) should use the CONSORT statement as a guide to preparing the manuscript (http://www.consort-statemen.org); - conflicts of interest should be clearly stated in the manuscript (see below).

The authors are encouraged to refer to national and international registries of trials in their papers (such as clinicaltrials.gov), where applicable.

Review articles

Review articles, systematic reviews and meta-analyses should not exceed 3000 words (excluding abstract, references, tables and legends). The manuscript should contain subheadings. A maximum of 6 tables and figures (in total) are allowed. Please provide titles above and legends below these elements. The abstract should not exceed 250 words and should be structured: background, methods, results, conclusions, with the exception of a non-systematic review, which may contain a non-structured abstract. No references should be included in the abstract. Authors should provide a minimum of 3 keywords, a running title, and a list of not more than 70 references. The authors are encouraged to refer to national and international registries of trials in their papers (such as clinicaltrials.gov), where applicable.

Editorials

Editorials are always commissioned by the Editors and comment on one or more articles in the same issue of the Journal or to a subject with high news value. Editorials should not exceed 1500 words and may be unstructured. Please provide a minimum of 3 keywords and a list of not more than 30 references. Please include an informed consent statement from the patient described in the case.

Clinical problem-solving

These manuscripts consider the step-by-step process of clinical decision-making. Information about a patient is presented to an expert clinician or clinicians in stages (indicated by boldface type in the manuscript) to simulate the way such information emerges in clinical practice. The clinician responds (in regular type) as new information is presented, sharing his or her reasoning with the reader. The text should not exceed 2500 words, and there should be no more than 15 references. Please include an informed consent statement from the patient described in the case.

Research news

Research news should be a review of a manuscript which has appeared in the past two months. It contains sections on why this study was done, the research question, how this was investigated, conclusions and the impact of the study on clinical practice. The text should not exceed 800 words with a maximum of 5 references. Contributions for this section will be commissioned; however, inquiries about contributions can be sent to a.p.vlaar@amc.uva.nl.

Clinical images

A clinical image should contain one or two pictures with a legend and a short case history, and should preferably not be referenced. The manuscript should succinctly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. Please provide a minimum of 3 keywords. The text should not exceed 500 words. Please include an informed consent statement from the patient described in the case.

Photo quiz

In this section relevant images for critical care medicine (e.g. flow and pressure curves of mechanical ventilation or haemodynamic indices, radiological images or laboratory results) will be accompanied by a short introduction of the context. The introduction will be followed by ‘what is your diagnosis?’ The answer will include a brief discussion of the literature. A photo quiz should not exceed 500 words and contain no more than two figures, and five references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

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A book review should not exceed 300 words. Please mention in the header: title, author, edition and year. Scan the cover in high resolution (300 dpi/1 mb) and send with the text. With an online review, the cover can usually be downloaded. Details with the cover: title, author, edition, year, publisher, number of pages, price and ISBN number. Conclude with the name and affiliation(s) of the reviewer.

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General information

Each manuscript should be accompanied by a cover letter stating the following: the complete postal address, email address and telephone number of the corresponding author and, if it is a resubmission, the previous Neth J Crit Care number and year. The language of the journal is British English. Authors who are unsure of proper English usage should have their manuscript checked by someone proficient in the English language. All text should be double spaced. The manuscript pages, including references and legends, should be sequentially numbered throughout.
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- The title of the manuscript should be in typeface Times New Roman, size 20. With the exception of the first word and proper nouns, initial capitals are not used in the title.
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- The names of hospitals should be written in English.
- Write 'the Netherlands' without capitalising the t.
- Generally, abbreviations should not be used in the title (see Table of standard abbreviations for exceptions).
- The corresponding author only provides his/her email address on the title page.
- Please provide a minimum of three keywords and a running title.
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- Headings must be in bold. Use no more than two levels of headings.
- Paragraphs starting immediately under headings and subheadings should begin at the left margin. Subsequent paragraphs should be indented.
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- Use British English spelling – except in titles of institutions that have chosen to use US spelling, e.g. Academic Medical Center, Amsterdam. Examples: anaemia (instead of anaemia), oesophagus (instead of esophagus), litre (instead of liter), colour (instead of color), labelling (instead of labeling), practice (noun), and practise (verb). This should be used consistently. Use the s-form spelling, e.g. minimisations, re-formation.
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- References are numbered sequentially in the text and placed in square brackets after the punctuation. […]
- Genus names should be written in italics, e.g. Staphylococcus aureus, S. aureus.
- Numbers under 10 must be spelled out except for measurements with a unit (10 mmol/l) or age (4 weeks old), or when in a list with other numbers (5 mice, 6 rats, 12 gerbils).
- When referring to tables or figures in the text, use italics; do not use a capital letter, e.g. see table 2.

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- Do not use spaces, tabs or hard returns in tables;
- Each piece of data must be contained in its own cell;
- Numbers and percentages are presented in the same cell;
- Tables should always be cited in the text in consecutive numerical order;
- For each table, please supply a title explaining the components of the table;
- Any abbreviations used in the table must be defined in a legend;
- Tables should not exceed the printed area of the page (174 x 234 mm).

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Table of commonly used abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ALI</td>
<td>acute lung injury</td>
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<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
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<tr>
<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
</tr>
<tr>
<td>BIPAP</td>
<td>biphasic positive airways pressure</td>
</tr>
<tr>
<td>ECMU</td>
<td>coronary care unit</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>ETCO2</td>
<td>end-tidal carbon dioxide</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IC</td>
<td>intensive care</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>INR</td>
<td>international normalised ratio</td>
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<tr>
<td>IPPV</td>
<td>intermittent positive pressure ventilation</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<tr>
<td>MODS</td>
<td>multorgan dysfunction syndrome</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PACU</td>
<td>post anaesthesia care unit</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>PET</td>
<td>position emission tomography</td>
</tr>
<tr>
<td>SIRS</td>
<td>severe adult respiratory syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>sequential organ failure assessment</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
</tr>
</tbody>
</table>