CASE 2: 74-YEAR-OLD MAN IN A LONG-TERM CARE FACILITY WITH FEVER AND ABDOMINAL PAIN

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Initial Presentation

In August 2019, a 74-year-old white man from Sicily was transferred from a long-term care facility (LTCF) to the emergency department for fever and abdominal pain that had appeared within the previous 3 hours. His past medical history included dyslipidemia, type 2 diabetes, alcohol abuse, and a recent acute exacerbation of chronic obstructive pulmonary disease for which he received a 7-day course of antibiotic therapy with cephalosporins and quinolones.

Case Work-Up

At hospital admission, the physical examination revealed hypotension (85/60 mm Hg), tachycardia (120 pulse/min), and fever (39°C/102.2°F). Cardiac auscultation revealed systolic murmur +/++ in the aortic area. Thoracic auscultation was normal. Abdomen was painful and tense. Abdomen X-ray showed sub-diaphragmatic air. His complete blood count revealed:

- White blood count (WBC) 18,500/mm^3 (84% Neutrophils)
- Hemoglobin (Hb) 11 gr/dL
- Creatinine level was 1.0 mg/dL
- Bilirubin level was 0.7 mg/dL
- Lactate level was 1 mmol/L

The patient was diagnosed with acute abdomen related to perforation. An emergent laparotomic surgery was performed; the intraoperative diagnosis was secondary peritonitis related to perforated gastric cancer. He underwent partial gastrectomy plus abdominal washing. External peritoneal drainages were inserted. Blood cultures and intraoperative material were sent to the microbiology laboratory (micro-lab). Empirical antibiotic therapy with amoxicillin-clavulanic acid was started. At 48 hours post-surgery, the patient was still febrile, with blood pressure (BP) 100/60 mm Hg. His complete blood count showed WBC 22,500/mm^3.

Challenge Question 1. What is the best step for management?

A. **Start empirical antifungal therapy because the patient has several risk factors for intra-abdominal candidiasis, including diabetes**
B. **Administer broader antibiotic therapy including coverage against extended spectrum beta-lactamase (ESBL)**
C. **Wait for pending cultures**
D. **Administer broader antibiotic therapy including coverage against *Pseudomonas aeruginosa***

Discussion

A. **Start empirical antifungal therapy because the patient has several risk factors for intra-abdominal candidiasis, including diabetes.** Empirical antifungal therapy is administration of antifungal agents in patients with signs and symptoms of infection along with intra-abdominal-specific risk factors, which include recurrent abdominal surgery, gastrointestinal tract perforations (untreated within the first 24 hours) or gastrointestinal anastomosis leakage[1]. Additional nonspecific risk factors include acute renal failure, central venous catheter placement, total parenteral nutrition, intensive care unit (ICU) stay, prolonged broad-spectrum antibacterial therapy and severity of sepsis, diabetes, and immunosuppression. Since our patient has a community intra-abdominal infection without specific risk factor for intra-abdominal candidiasis (his gastrointestinal perforation was treated within the first 3 hours) an empirical antifungal therapy could be avoided.
B. **Administer broader antibiotic therapy including coverage against ESBL.** A broader antibiotic therapy including coverage for ESBL producing Enterobacterales can be considered. Indeed, the risk of infection

with ESBL-producing organisms is higher in male patients and has been described to rise with age, previous use of antibiotics, recent hospitalization, or admission from a LTCF[2].

C. **Wait for pending cultures.** Since the patient was hemodynamically stable, waiting for pending results can also be considered as a suitable option.

D. **Administer broader antibiotic therapy including coverage against *Pseudomonas aeruginosa.*** To the best of our knowledge, there is no study specifically addressing risk factors for developing *Pseudomonas aeruginosa* intra-abdominal infection. However, previous reports focusing on patients with gram-negative bloodstream infections found that age >90 years, receipt of antimicrobials within 30 days, and presence of a central venous catheter or urinary device were all specific risk factors for *P. aeruginosa* infections at hospital admission[3]. This patient has only one specific risk factor for *P. aeruginosa.* Therefore, the probability for *P. aeruginosa* is very low (less than 10%), and an empirical anti-*Pseudomonas* agent could be avoided.

Correct answer: Both **B** and **C** are suitable management options.

Case Management

For this patient, the clinician followed strategy B. On Day 3 after surgery, antibiotic treatment was switched to meropenem 1 g every 8 hours.

On Day 4 after surgery, micro-lab informed us that a third-generation cephalosporin resistant *Escherichia coli* (subsequently characterized as an ESBL-producing isolate) was growing from both blood cultures and the intra-abdominal specimen. After implementing a carbapenem-based regimen, the patient experienced good clinical evolution with disappearance of fever and reduction of leukocytosis and inflammatory markers.

On Day 5, the patient experienced sudden appearance of new abdominal pain and fever with stable hemodynamic conditions. He underwent a new emergent relaparotomy with clinical evidence of upper gastrointestinal dehiscence and peritonitis for which a continuous peritoneal lavage was performed. Intra-abdominal samples were not collected. However, an intra-abdominal sample obtained from the drain implanted from 12 hours was sent to micro-lab.

Challenge Question 2. While waiting for culture results, should empirical antifungal treatment be considered in addition to empiric antibacterials?

A. Yes

B. No

Discussion

In this case, we waited for culture results. Indeed, empirical antifungal therapy is usually suggested in patients with complicated intra-abdominal infection and at least one specific risk factor for intra-abdominal candidiasis[1] (eg, recurrent abdominal surgery, gastrointestinal tract perforation, and/or multifocal colonization) plus unstable hemodynamic conditions. In the present case, although specific risk factors were present, the patient was hemodynamically stable, delineating an overall picture in which the decision whether or not to administer empirical antifungals remains controversial.

Case Continued

On Day 6, the micro-lab informed us that a yeast was growing from the drainage sample. After obtaining information about yeast growth, a therapeutic change was considered.

Challenge Question 3. Which statement is true?

- **A. *Candida* isolated from the intra-abdominal cavity always represents colonization and should not be treated.**
- **B. In order to confirm intra-abdominal candidiasis (IAC) diagnosis, non-culture-based methods should be performed.**
- **C. Any isolates obtained from drainage should be treated, since they always represent infection.**
- D. **Surgical or early drainage intra-abdominal samples are useful to diagnose IAC as blood cultures are positive in a low proportion of patients.**

Discussion

A. ***Candida* isolated from the intra-abdominal cavity always represents colonization and should not be treated.** The meaning of *Candida* isolation in the abdominal cavity is controversial, particularly in the context of polymicrobial infections. In fact, there is no gold standard for intra-abdominal candidiasis diagnosis. There are not even consistent criteria to discriminate between colonization and infection. However, when *Candida* is isolated from intra-abdominal samples or obtained surgically, it should be considered significant for IAC, since positive cultures are associated with higher mortality[5]. In our case, surgically obtained samples were not available (see comments to subsequent answers).

B. **Only non-culture-based methods can help clinicians to perform IAC diagnosis**. Although non-culture-based methods can help clinicians confirm or rule out a diagnosis of IAC, they cannot replace conventional diagnosis for IAC as of today. For example, in a recent study performed by Tissot, et al[6],

levels of beta- D-glucan > 82.6 pg/mL in serum were useful to differentiate between infection or colonization. However, the specificity of the test was lower than 50%.

C. **Any isolates obtained from drainage should be treated, since they always represent infection.** *Candida* isolation may be considered significant if yeasts are recovered from a drain inserted within 24 hours from the cultures. On the other hand, samples obtained through drainage tubes after the first 24 hours post-implantation are neither representative nor valuable for intra-abdominal candidiasis diagnosis[7] (they are only useful for studies of colonization).
D. **Surgical or early drainage intra-abdominal samples are useful to diagnose IAC as blood cultures are positive in a low proportion of patients.** Intra-abdominal samples are the mainstay for diagnosis of IAC. Blood cultures are positive in only 10-20% of patients with IAC[8].

Correct answer: D.

Case Continued

In the present case, an echinocandin was added to antibacterial therapy, and on Day 7 it was confirmed that *C. albicans* grew from the drainage sample.

Challenge Question 4. Waiting for susceptibility test results, do you agree with this decision to start treatment with an echinocandin?

A. No, I would have started empirical fluconazole
B. I would have preferred fluconazole in areas with low prevalence of fluconazole-resistance

Discussion

A. **No, I would have started empirical fluconazole.** According to experts, lipid formulations of amphotericin B or echinocandins are the preferred empirical treatment choice in unstable, critically ill patients (and/or with previous exposure to azoles)[7].
B. **I would have preferred fluconazole in areas with low prevalence of fluconazole-resistance.** Fluconazole may be considered in stable patients without previous azole exposures in settings with a low prevalence of fluconazole resistance. In the present case, although the patient was stable, we considered that resistance to fluconazole in *C. albicans* in our center is not negligible, and we ultimately decided to start treatment with an echinocandin.

Correct answer: B.

On Day 8, susceptibility test results became available, with the isolated *C. albicans* being susceptible to fluconazole. Therapy was de-escalated to fluconazole (800 mg initial dose followed by maintenance doses of 400 mg), with favorable clinical response in the following days.

Challenge Question 5. For how long should antifungal treatment be continued?

A. **For 10-14 days**
B. **For 21-28 days**
C. **Until negative inflammatory markers**

Discussion

For intra-abdominal candidiasis, the duration of therapy should be driven by the adequacy of source control and the clinical response[7]. In this case, the patient experienced a favorable response to the step-down fluconazole therapy. Therefore, it is reasonable to follow the general guidance to discontinue therapy after 14 days for uncomplicated cases of invasive candidiasis[7]. Checking inflammatory markers is not necessary; the clinical assessment is enough.

Correct answer: A.

Case Outcome

Eventually, the patient improved, and antifungal treatment was discontinued after 14 days. Subsequently, the patient was transferred to a surgery ward and then discharged home in good condition.

Summary of Special Issues Regarding Intra-Abdominal Candidiasis

The present case shows how a peculiar entity such as intra-abdominal candidiasis is managed in our center. One important challenge for the management of intra-abdominal candidiasis is the lack of a universal definition (although a European initiative[9] has been recently taken to develop standard definition of invasive fungal diseases in non-neutropenic adults in intensive care units). Another critical aspect is source control, which is the mainstay of the therapeutic approach to intra-abdominal candidiasis together with appropriate antifungal treatment[7]. Indeed, an association between delayed source control and mortality was observed in patients with complicated intra-abdominal infections. In this regard, it is widely recognized that source control should be obtained within 6-12 hours in unstable patients[10]. Nonetheless, some controversy remains regarding its exact timing, with some recent evidence suggesting the possible necessity for further reduction of this time window.

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