

Dear Reviewer,

Thank you very much for your revision.

Here I attach the answer to all your comments and suggestions. We have already modified the manuscript, adding all the data you had kindly asked for.

Best regards,  
Aleksandra Gładyś

### **SPECIFIC COMMENTS TO AUTHORS**

In this case report, authors report the management of two solid organ transplanted patients with PTLT and urinary and pulmonary tract infections during ICTH, and discuss the role of interventions including the reduction of immunosuppression therapy, doses of chemotherapeutics and GCS-F used in the prevention of neutropenic fever, in preventing infectious complications. However, this case report has some problems as following:

In the TREATMENT Sections, urinary and pulmonary tract infections (Page 8, Line 16-19) and bloodstream infections (Page 14, Line 9-10) are mentioned. Can authors give more data regarding urinary and pulmonary tract infections and antibiotic therapy?

(1) Are the pathogenic pathogens derived from sputum or urine, the culture or the detection of nucleic acids?

#### CASE 1 (proofreading p. 8):

Blood culture showed a growth of *Staphylococcus aureus* (sensitive to ciprofloxacin) and *Klebsiella pneumoniae* ESBL (+) (resistant to ciprofloxacin and co-trimoxazole, but sensitive to carbapenems and aminoglycosides).

Three days later, there was a worsening of dyspnea, cough and decreased oxygen saturation of 88%-90%, without an increase in the concentration of inflammatory markers. *Pneumocystis jirovecii* infection was suspected and a smear from the epiglottis was taken for the examination.

### CASE 2 (p. 9)

The presence of multi-drug-resistant bacteria was found in the blood cultures. The first blood culture revealed *Stenotrophomonas maltophilia* and ESBL *Escherichia coli* (resistant to beta-lactams, cephalosporins and co-trimoxazole but sensitive to carbapenems) and 5 days later the second blood culture showed MRCNS *Staphylococcus lentus* and MRCNS *Staphylococcus hominis* (resistant to beta-lactams, carbapenems, cephalosporins but sensitive to aminoglycosides).

(2) What are the in vitro susceptibilities of bacteria?

### CASE 1 (p. 8):

Blood culture showed a growth of *Staphylococcus aureus* (sensitive to ciprofloxacin) and *Klebsiella pneumoniae* ESBL (+) (resistant to ciprofloxacin and co-trimoxazole, but sensitive to carbapenems and aminoglycosides).

### CASE 2 (p. 9)

The presence of multi-drug-resistant bacteria was found in the blood cultures. The first blood culture revealed *Stenotrophomonas maltophilia* and ESBL *Escherichia coli* (resistant to beta-lactams, cephalosporins and co-trimoxazole but sensitive to carbapenems) and 5 days later the second blood culture showed MRCNS *Staphylococcus lentus* and MRCNS *Staphylococcus hominis* (resistant to beta-lactams, carbapenems, cephalosporins but sensitive to aminoglycosides).

(3) What are the name, dosage and time antibiotic therapy?

### CASE 1 (p. 8):

Broad-spectrum antibiotic therapy with meropenem (1 g for every 12 h) and amikacin (500 mg once a day) was administered. Three days later, there was a worsening of dyspnea, cough and decreased oxygen saturation of 88%-90%, without an increase in the concentration of inflammatory markers. *Pneumocystis jiroveci* infection was suspected and a smear from the epiglottis was taken for the examination. Additionally, co-trimoxazole was administered intravenously at a dose of 960 mg twice daily.

### CASE 2 (p. 9)

After therapy with meropenem (1 g every 8 h) and amikacin (500 mg daily) for ten days, CRP level decreased to 6.0 mg/L. Subsequently, ICTH was continued with reduced doses and after the

second R-IVAC cycle, neutropenia developed with negative blood cultures (performed 3 times). Because of the clinical symptoms (fever, dyspnoea, weakness) and high CRP level 173 ng/mL intravenous therapy with vancomycin (2 g every 8 h) was started. As there was no clinical improvement (repeated negative blood cultures), after 7 days, colistin was administered intravenously (2 mL units every 8 h) with a good clinical response (CRP 15.8 mg/L).

(4) How much are the values of serum inflammatory markers (such CRP, procalcitonin) before and after antibiotic treatment.

CASE 1 (p. 8):

CRP 217 mg/L and procalcitonin 40.1 ng/mL (before antibiotic treatment) and CRP 14.8 mg/L and PCT 0.4 ng/mL (after treatment).

CASE 2 (p. 9)

CRP level was 164 mg/L (before treatment). After the therapy, CRP level decreased to 6.0 mg/L.

After the second R-IVAC cycle, neutropenia developed with negative blood cultures (performed 3 times). Because of the clinical symptoms (fever, dyspnoea, weakness) and high CRP level 173 ng/mL intravenous therapy with vancomycin (2 g every 8 h) was started. As there was no clinical improvement (repeated negative blood cultures), after 7 days, colistin was administered intravenously (2 mL units every 8 h) with a good clinical response (CRP 15.8 mg/L).

(5) Page 14, Line 9-10: In numerous bloodstream infections, are all types of microorganisms (*Stenotrophomonas maltophilia*, ESBL *Escherichia coli*, MRCNS *Staphylococcus lentus*, and MRCNS *Staphylococcus hominis*) considered to be pathogenic pathogens? Why?

Due to the clinical condition of the patient (grade 4 anemia and neutropenia as a result of ICHT, with additional infectious complications) we considered these bacteria found in the blood culture during the infection as pathogenic.

Here I enclose the whole "TREATMENT" section for both patients, in order to give a clear picture of the antibiotic therapies:

## **TREATMENT**

**CASE 1:** The patient signed informed consent for ICTH and started R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), as initial rituximab monotherapy increases the risk of recurrence and usually does not bring complete remission in monomorphic PTLD<sup>[9]</sup>. Beyond slight, local upper limbs oedema, the patient tolerated the applied ICTH quite well. Night sweats subsided after the second R-CHOP cycle. Neutropenia and anaemia (requiring transient blood transfusion) were manageable. An episode of atrial fibrillation occurred after the second cycle. The immunosuppression, as well as the doses of chemotherapeutics, were reduced (mycophenolate mofetil was discontinued) due to episodes of prolonged pancytopenia. The G-CSF treatment (filgrastim) in the secondary prevention of neutropenic fever (NF) was used. Regardless of the use of GCS-F and *Pneumocystis jiroveci* prophylaxis (with co-trimoxazole), after the fifth cycle, the patient developed grade 4 neutropenia with symptoms of febrile neutropenia. There was an increase in the concentration of inflammatory markers: CRP 217 mg/L and procalcitonin 40.1 ng/mL. Empirical antibiotic therapy with ciprofloxacin was started. After one week, regardless of neutrophil recovery, inflammatory parameters were still elevated and the symptoms (fever, weakness and dysuria) persisted. Blood culture showed a growth of *Staphylococcus aureus* (sensitive to ciprofloxacin) and *Klebsiella pneumoniae* ESBL (+) (resistant to ciprofloxacin and co-trimoxazole, but sensitive to carbapenems and aminoglycosides). Broad-spectrum antibiotic therapy with meropenem (1 g for every 12 h) and amikacin (500 mg once a day) was administered. Three days later, there was a worsening of dyspnea, cough and decreased oxygen saturation of 88%-90%, without an increase in the concentration of inflammatory markers. *Pneumocystis jiroveci* infection was suspected and a smear from the epiglottis was taken for the examination. Additionally, co-trimoxazole was administered intravenously at a dose of 960 mg twice daily. Few days later, a significant improvement of the patient's clinical condition with a decrease of inflammatory markers concentration (CRP 14.8 mg/L and PCT 0.4 ng/mL) was observed. The patient recovered, however with persisting impaired graft function. The doses of ICTH were reduced by 30% in the next 2 cycles. Despite dose reduction, the therapy had been terminated because of grade 4 neutropenia.

PET-CT performed after the seventh cycle revealed active lesions in sub- and infraclavicular area with the avidity of 4 points in the Deauville five-point scale. The patient started involved-field radiation therapy (3D-IMRT, Dc = 30 Gy/df = 3) of the residual disease.

**CASE 2:** The patient signed informed consent for ICTH with 4 cycles of R-CODOX (rituximab, cyclophosphamide doxorubicin, vincristine, cytarabine) followed by R-IVAC scheme (rituximab, ifosfamide, cytarabine, methotrexate) and started the treatment. After the 1st cycle of R-CODOX therapy, symptoms of neutropenic fever appeared. The presence of multi-drug-resistant bacterias

was found in the blood cultures. The first blood culture revealed *Stenotrophomonas maltophilia* and ESBL *Escherichia coli* (resistant to beta-lactams, cephalosporins and co-trimoxazole but sensitive to carbapenems) and 5 days later the second blood culture showed MRCNS *Staphylococcus lentus* and MRCNS *Staphylococcus hominis* (resistant to beta-lactams, carbapenems, cephalosporins but sensitive to aminoglycosides). CRP level was 164 mg/L. After therapy with meropenem (1 g every 8 h) and amicin (500 mg daily) for ten days, CRP level decreased to 6.0 mg/L. Subsequently, ICTH was continued with reduced doses and after the second R-IVAC cycle, neutropenia developed with negative blood cultures (performed 3 times). Because of the clinical symptoms (fever, dyspnoea, weakness) and high CRP level 173 ng/mL intravenous therapy with vancomycin (2 g every 8 h) was started. As there was no clinical improvement (repeated negative blood cultures), after 7 days, colistin was administered intravenously (2 mL units every 8 h) with a good clinical response (CRP 15.8 mg/L). During the whole ICTH the patient received red blood cells transfusions (14 units in total) because of grade 4 anaemia.