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EDITORIAL

Facing urosepsis- the most deadly of all urological diseases

Editorial comment to 'Community-onset urosepsis; incidence and risk factors for 30-day mortality- a retrospective cohort study', by Holmbom M. et al.

Sepsis is the deadliest disease encountered by urologists. In the present issue of Scand J Urol, Holmbom and colleagues report the mortality of community-acquired urosepsis in Sweden to be 14% and for patients with Gram-positive pathogens the mortality was as high as 33% [1]. We would like to put this very important publication into context.

Clinical situation

All urologists share the experience of being called to the ward or the postoperative unit because a patient is shivering with chills and has fever. The nurse is concerned with the patient's oxygen saturation. You inspect the patient's skin colour, you check the patient's cognitive function with a few questions and you check the amount and concentration of urine in the bag at the side of the bed. While doing this you hold the patient's wrist and count the heart rate, check the refilling of capillaries, look at the respiratory movements and count the respiration rate. Within seconds, you have checked for SIRS (systemic inflammatory response syndrome) and q-SOFA (quick-sequential organ failure assessment) criteria and made the diagnosis of sepsis. A few minutes later, you get the lab data with tests of organ function. If needed, you order empirical antibiotic treatment according to local protocol and resistance data, implement supportive treatment with fluids and oxygen and consider measures to obtain source control. If there are signs of organ failure, you will most likely refer the patient to the intensive care unit for further supervision and treatment. If the patient deteriorates and you see him/her again, there might be skin necrosis at fingers, toes, or even penis. At some time point, you may be asked if it is time to stop intensive care.

Sepsis and pepsis

Sepsis means disintegration of tissue by putrefaction as opposed to physiological digestion or pepsis [2]. The clinical condition was described already by ancient Egyptians and later by Hippocrates. Several symptoms and findings occur simultaneously and hence the condition was called a syndrome. When pathogens were identified in the bloodstream of patients with sepsis (many centuries later), the condition was regarded a disease. However, still today, despite sophisticated diagnostic tools, pathogens are only detected in the bloodstream in about a third of patients with clinical signs of sepsis.

The SIRS definition uses central hemodynamic data and respiration rate as diagnostic criteria for sepsis together with body temperature and levels of white blood cells. For the two criteria most typically related to the immune response, the values can be either significantly higher or lower than normal. Current definitions recognize sepsis as a dysregulated immune response. In 1994, an expert committee of the European Society of Intensive Care Medicine developed the SOFA score [3]. The committee recognized that organs tend to fail in an order or sequence and introduced the term 'sequential'. They also recognized that disease progression may occur rapidly and recommended that antibiotic treatment and source control, for example inserting a nephrostomy tube in case of obstructive pyelonephritis, should take place within one hour after diagnosis [4].

Several scores have been developed to facilitate early detection, diagnosis and prediction of the disease course, i.e. NEWS1 and −2, q-SOFA, APACHE and others. The most important biomarker is blood lactate. An elevated lactate value in serum is a sign of anaerobic metabolism caused by reduced oxygen delivery to cells. Numerous studies evaluate possible tumour markers in urosepsis i.e. procalcitonin and proadrenomedullin [5]. The most common types of organ failure in patients with severe sepsis are cardiovascular, respiratory, and renal dysfunction [6].

Pathophysiology

We do not know which mechanisms bring about the dysregulated immune response leading to sequential organ failure and death. In patients who die of sepsis the most common autopsy findings in kidneys are acute papillary necrosis. Other organs show signs of bleeding, circulatory failure and focal necrosis [7]. Clinicians should remember that the skin is the largest organ in the body and pathophysiological changes are easily detectable. Although diagnostics and treatment monitoring concentrate on central hemodynamics, what matters most for life and death of cells in peripheral tissues is the delivery of oxygen through capillaries. Endothelial cells and pericytes have key roles in the local regulation of capillary flow. Interestingly, researchers have also detected a dysregulation of microcirculation in research animals as well as in patients with sepsis [8]. Endothelial dysfunction also have a role in immunological disorders.

Capillaries do not deliver oxygen at the doorstep to be picked up by peripheral cells. Oxygen molecules in erythrocytes have to diffuse across membranes and according to the Norwegian Nobel prize winner in 1922 there is a critical distance called the Krogh's diameter beyond which the oxygen molecules will not reach their addressee. If capillaries obliterate or there is significant interstitial oedema, the

distance from a cell to the nearest capillary may become longer than the Krogh's radius and cells will die.

Endothelial cells and pericytes do have a role in the pathogenesis of sepsis. Assessment of microcirculation might provide prognostic aid and endothelial cells and pericytes might become future treatment targets in sepsis [8].

Perspectives

The mortality of community-acquired urosepsis in Sweden observed by Holmbom et al. was significantly higher than the mortality of hospital-acquired sepsis in preliminary data from the EAU-SERPENS study as well as in other studies [9]. The most likely explanation for the difference in mortality between community and hospital-acquired sepsis is that the sequential organ deterioration has proceeded for a longer time outside the hospital, due to delayed diagnosis by patients and primary health care workers alike.

Our most important measure to reduce the mortality from community-acquired sepsis is to improve early diagnosis and treatment by raising awareness in the general public, among patients and in staffs working in community health care. The difference in mortality between community- and hospital-acquired sepsis is probably larger in countries with less well-developed community health care than Sweden. Holmbom's findings also underline the importance of tailoring empirical antibiotic treatment according to local resistance data and microbiological spectra, which is the meaning of empirical treatment. Early and effective empirical antibiotic treatment is crucial for a successful outcome of sepsis.

Unfortunately, the risk of dying from sepsis is expected to increase in the coming decades. According to the O'Neil report this will occur because of increased antibiotic resistance [10]. With poor prospects of new antibiotics being introduced in the near future, our chances to effectively treat sepsis as well as other urological infections, will diminish and mortality will increase. This is the dramatic core message of the O'Neil report and the main argument for antibiotic stewardship. Stewardship means prudent use of antibiotics to prevent further development of antibiotic resistance. Meanwhile, urologists should avoid contaminated procedures that require prophylaxis with broad-spectrum antibiotics. Replacing transrectal with transperineal prostate biopsy is one good example. In conclusion, since urosepsis is a highly lethal disease and accounts for one third of all sepsis cases, we urge urologists to engage in research to further explore the pathophysiology of sepsis and identify new biomarkers, treatment targets and treatments.

Disclosure statement

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