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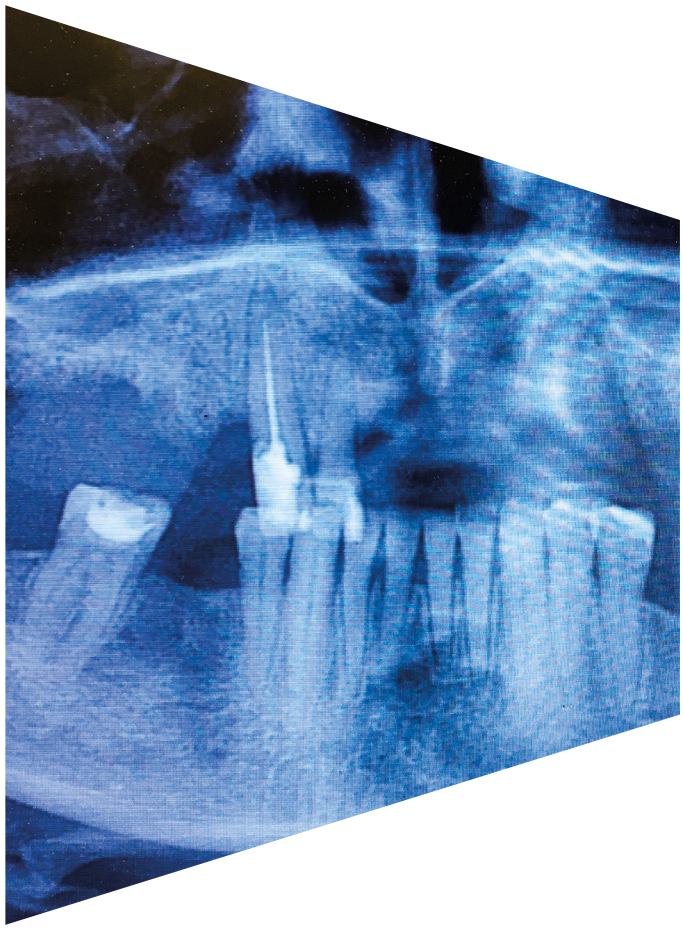

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CONTENTS

INVITED REVIEW ARTICLE

RESEARCH ARTICLES

REVIEW ARTICLES

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2020;3(1):7-10

INVITED EDITORIAL

It didn’t have to happen this way – what COVID-19 tells us about translational medicine

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Abstract

In this editorial I would like to invite the Readers to look at this situation with broader time frame in mind. I attempt to draw some conclusions from the COVID-19 pandemic that are relevant for the field of translational medicine. My perspective is that it didn’t have to happen this way and even worse, the same situation might repeat itself in the near future.

Keywords: COVID-19 · translational medicine · surgery

Citation

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In December 2019 people who were aware of the *Coronaviridae* family’s existence were mostly scientists [1]. Today, or four months later, we all are undergoing practical training in epidemiology, we seek information about the structure of the SARS-CoV-2 virus, non-scientific magazines publish the virus’ mortality rate, websites of banks and mobile phone service providers remind us about infection prevention methods and economics experts are convincing us that COVID-19 will not trigger a global recession [2].

In this editorial I would like to look beyond a quick analysis of the rapidly incoming information and invite the Readers to look at this situation with broader time frame in mind. My perspective is that it didn’t have to happen this way and even worse, the same situation might repeat itself in the near future.

Several years ago an analysis of parish archives in Gilowice (near Kraków) and Starogard Gdański revealed that 50% of the recorded deaths in the years 1880-1920 were of children < 7 years of age and of

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those 30% were children < 1 year of age [3-4]. At the time the average lifespan in that part of Europe was 25-35 years, there were about 1 billion people living on earth and we had essentially no methods of controlling epidemics of infectious diseases [5]. According to the archives, the leading causes of death were pertussis, tonsillitis, scarlet fever, "cough," pneumonia, dysentery, smallpox. Thanks to vaccinations, antibiotics and hygiene many of these diseases are not found in medical practice anymore, children die sporadically and the average lifespan today is approaching 80 years [6]. In contrast, the leading causes of death around the world today are cardio-vascular diseases, diabetes and cancer [7].

The last global pandemic was the Hong-Kong flu in the years 1968-1970 [8]. Infectious disease specialists could have felt that their mission was completed: pandemics disappeared, almost all of the deadly diseases were eradicated, treatment of the remaining and clinically significant infectious diseases (e.g. HIV, HCV, borreliosis) is so simple that it doesn't require specialized training [8-9]. Some went as far as to say that there is no need for infectious disease specialists anymore.

Unfortunately, in December 2019 in Wuhan (China) cases of a strange pneumonia were noted [10]. You know the rest of the story and we are still part of it today. It is a rather unpleasant feeling to lose control over the events, to be unable to influence the course of the disease (lack of effective treatment, lack of vaccine) and yet at the same time to have to implement drastic limitations of personal freedom in order to stop the pandemic [1, 11]. In practice we are now where we were almost 100 years ago, when the only methods of infection control available were: personal hygiene, isolation, quarantine, sanitary cordon around a city [12-13].

Suddenly the medical world returned to the age when the patient posed a significant danger to the health and life of the physician. In the recent decades we became convinced that our profession is safe and prestigious. Many of us accompany our patients in their agony and death. Indeed this is difficult depressing and may lead to professional burnout, however rarely causes the physician to feel that his/her life is in danger [14]. Now all this has changed and we hear or read about desperate reactions of medical personnel, e.g. trying to strengthen the immune system by using dietary supplements despite the lack of evidence for their effectiveness or seeking pre-exposure prophylaxis guidelines.

It is worth remembering that we witnessed a similar situation in 2002-2003 with the SARS-CoV-1 epidemic [15]. That was also the same time when a new technology became available, the *in silico* method, which led to the effective and safe anti-viral drugs for HIV and HCV [16]. Despite the availability of this new technology and other research tools neither drug nor vaccine against SARS were created. The reason for this situation is rather simple: it was completely not cost-effective [13].

Fortunately, scientists did not sit idly. Numerous particles and drugs with in vitro efficacy were synthesized in laboratories around the world against various viruses, including those from the *Coronaviridae* family. These research projects became stuck in the pre-clinical phases due to the lack of funding, time and volunteer patients. Today these same particles are cleaned of dust and once again re-challenged in terms of their effectiveness against the current biological threat (e.g. remdesivir) [17]. Funding is more likely available now, however for some of the patients there will unfortunately not be enough time [13].

It was predictable that the problem will return. Similar epidemics (MERS, flu virus) occurred as natural events in Southeast Asia and hemorrhagic fevers or retroviruses appeared in Sub-Saharan Africa [13]. Epidemics are somewhat like earthquakes: they do not happen daily and although we know that they will occur again, we are not able to predict when and where. Several years ago our attention was focused on the deadly Ebola virus [18-19]. This virus is known to science since 1976 and although we knew it is deadly, to this day we do not have any treatment or vaccine against it. The reason is once again financial: no government besides perhaps the USA or China is able to finance the costly and lengthy research projects and clinical trials. International pharmaceutical corporations do have the necessary funding, however they function for-profit [20].

A close relative of the Ebola virus is the Marburg hemorrhagic fever [19]. It is named after the central Germany city where the first cases were identified in 1967. The most likely source of the Marburg virus was in Uganda, thus none of us live safely on a lonely island [21].

From the virus' point of view, humans are its host and target. Since the first SARS outbreak in 2003 the global human population has increased by almost 2 billion, mostly in Asia. Today there are almost 9 billion of us on Earth and we travel significantly more often than in 2003, 1967 or 1918 [22]. Patients after organ transplantation also travel, just as those with HIV infection or on chronic immunosuppressive treatment. This is a good sign that patients are returning to their normal daily activity. However after becoming infected, these same patients may potentially replicate viruses for many months without any visible symptoms and therefore infect others. A repetition of the SARS or Marburg scenario is just a matter of time [1, 19].

Let's now draw some conclusions from the COVID-19 pandemic that are relevant for the field of translational medicine:

1. **We need an urgent, fast and non-commercial pathway for implementing medicines and vaccines for new biological threats. Clinical trials should be relatively inexpensive, financed by the taxpayers, not subject to the decisions ofshareholders and should last several months (not years).**
2. **We need to initially prepare candidate drugs (therapeutic molecules) against specific, potentially deadly virus families such as flu viruses, Coronaviridae, hemorrhagic fevers, retroviruses, etc. In case of a new outbreak, we need to urgently assess the effectiveness of the candidate drugs and to conduct clinical trials. Clearly this is a significant logistic challenge, however during an epidemic time costs lives.**
3. **Herpes virus eradication using vaccinations is a worthwhile goal. The Herpes endemic has the scope of a pandemic, therefore the lives of many people would be more comfortable and longer.**
4. **We need to prepare for an outbreak of a virus that, in theory, could be synthesized in vitro in order to achieve a political or demographic goal. Unfortunately such bioterrorism is technically feasible, though it is the subject for a completely separate article.**

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RESEARCH ARTICLE

Effect of a bicarbonate-buffered peritoneal dialysis solution on clinical and laboratory indices of dialysis

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Abstract

Background: Biocompatible fluids for peritoneal dialysis (PD) have been introduced to improve the dialysis adequacy and patient outcomes in end-stage renal disease. However, being buffered with lactate, these fluids may insufficiently correct metabolic acidosis and lead to changes in peritoneal structure. Bicarbonate buffered fluids might mitigate these complications. The aim of the study was to evaluate the influence of a bicarbonate dialysis fluid on clinical and laboratory indices of dialysis adequacy. **Methods:** Twenty PD patients treated with standard lactate solutions, were divided into two groups. Patients in the study group started treatment with a 34 mmol/L bicarbonate-buffered solution, whereas those in the control group continued on a lactate-buffered fluid. Assessment of urine output, dialysis ultrafiltration, hydration status as well as metabolic acidosis, dialysis adequacy and potential inflow pain was performed at baseline and at six weeks intervals for 24 weeks. **Results:** In the studied group, pH was 7.36 ± 0.03, HCO3 22.1 ± 1.8 mmol/l at baseline and 7.36 ± 0.04, and 21.2 ± 2.3 mmol/l at the end of the study, while in the control group the pH was 7.35 ± 0.12, with HCO3 22.2 ± 1.4 mmol/l, and 7.40 ± 0.03, and 22.3 ± 1.8 mmol/l, respectively. No statistically significant differences were noted. Dialysis effectiveness, measured as urea Kt/V, urine output and dialysis ultrafiltration did not differ between the groups, either at baseline or at the study termination. Only one patient in the studied group reported inflow pain and following conversion to bicarbonate-buffered PD fluid he reported reduction of its intensity. **Conclusion:** Bicarbonate-buffered PD solution appears to be similar to standard fluid in terms of the impact on residual renal function and ultrafiltration as well as on acid-base balance and infusion pain. Longitudinal studies are needed to assess the long-term advantages of this biocompatible solution in PD patients.

Keywords: peritoneal dialysis · acid-base balance · end-stage renal failure · bicarbonate-based solutions

Citation

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Introduction

Peritoneal dialysis (PD) is a method of renal-replacement therapy (RRT) utilized in patients with end-stage renal disease (ESRD). As the name suggests, in PD the peritoneum acts as the dialysis membrane. This mode of treatment is as effective as hemodialysis and can serve as a 'bridge' to renal transplantation or a life-long RRT treatment. Peritoneum separates the compartment of dialysis fluid from the blood compartment of peritoneal capillaries. Due to its semi-permeable structure, it allows for removal of uremic toxins as well as for restoring the electrolyte and acid-base balance.

Standard dialysis fluids are sterile solutions containing electrolytes, lactate ions and glucose at various concentrations. Such composition normally allows for sufficient patient dehydration and detoxification in the course of ESRD. However, due to its non-physiologic lactate buffer and the presence of glucose degradation products (GDP) its use is complicated by impairment of immunologic mechanisms of the peritoneum, and progressive fibrosis and thickening of the membrane with a concomitant loss of mesothelial cells [1]. Insufficient correction of metabolic acidosis leads to enhanced muscle catabolism, decreased albumin synthesis, and chronic low-grade inflammation.

New dialysis fluids are buffered with bicarbonates and are thought to mitigate the above complications [2-3]. Moreover, through improvement of the local peritoneal biocompatibility, they might positively affect dialysis adequacy [3]. However, despite being approved for use these new PD fluids have not been utilized in Poland so far. Therefore, the major aim of the current study was to compare novel PD solutions buffered with 34 mmol/l bicarbonates and the standard lactate-buffered fluids, in terms of clinical and biochemical adequacy. Particular aims were to assess the impact of a bicarbonate-buffered solution on the correction of metabolic acidosis and on improving the patient's hydration status, depending on patient residual renal function, and the presence of co-morbidities, as well as to evaluate the influence of the studied fluids on the sensation of abdominal pain during dialysis.

Material and Methods

This was a prospective evaluation of 20 patients treated at a single center with continuous ambulatory peritoneal dialysis (CAPD). All patients were initially dialyzed on a standard, neutral pH, 35 mmol/L lactate-buffered fluid (Balance, Fresenius, Germany). The patients who were similar in terms of age, sex, history of diabetes, urine output and dialysis adequacy so far were matched into pairs. Within each pair, the patients were randomly assigned to either start treatment with a 34 mmol/L bicarbonate-buffered solution (BicaVera, Fresenius, Germany) or to continue using the standard PD fluid. This way we obtained 2 equal groups of 10 participants each. All participants provided informed consent to participate in the study, and the study protocol was approved by the local Ethics Committee (NKBBN 212/2019).

Prior to the start of the evaluation (baseline) and at 6-week intervals, the following variables were analyzed: the clinical assessment of hydration status, urine output, dialysis ultrafiltration, acid-base balance (via capillary blood gas tests) as well as routine laboratory parameters . Hydration status was also assessed through bioimpedance spectroscopy (Body Composition Monitor, Fresenius Medical Care, Germany) and was presented as liters of over- or dehydration. Moreover, at 12-week intervals, indices of dialysis adequacy (urea Kt/V, creatinine clearance), protein turnover (normalized protein catabolic ratio, nPCR) and of transmembrane transport status (peritoneal equilibration test) were checked. Inflow pain was assessed using a visual analog scale (VAS). Results were expressed as means with standard deviations or medians with interquartile ranges, as appropriate. The normality of distribution was verified with the Kolmogorov-Smirnov test. A p-value of < 0.05 was considered statistically significant. Comparisons between two groups were assessed with a Student's unpaired t-test or Mann-Whitney test, as appropriate. The statistical analysis was performed using the Statistica software version 13.3 (StatSoft Inc., United States).

Results

The baseline characteristics of the studied groups are depicted in Table 1. Of the 20 patients in our sample, 11 were female.

Majority of patients in both groups took calcium carbonate and loop diuretics which affect acid-base balance and diuresis, respectively. However, their doses were not modified during the study period. There was one episode of peritonitis in the studied group, effectively treated with standard therapy, but the patient was excluded from the study. Another patient from the control group underwent kidney transplantation and did not complete the study. Therefore, 18 patients remained for the final evaluation, nine in each group.

Considering capillary blood acid-base balance, in the bicarbonate group, pH equaled 7.36 ± 0.03, while

Table 1. Baseline clinical characteristics of the studied groups; UF – dialysis ultrafiltration

	Bicarbonate group (n = 10)	Control group (n = 10)	p-value
Age (years)	54 (36-58)	56 (47-65)	0.36
Sex (M/F)	3/7	4/6	
Dialysis vintage (months)	30 ± 18.7	44 ± 29.9	0.23
Diuresis (ml/day)	840 ± 685	1200 ± 640	0.34
UF (ml/day)	1270 ± 365	1170 ± 411	0.57
Hydration status (L)	1.51 ± 1.12	2.24 ± 1.23	0.18
Kt/V (renal)	0.81 ± 0.77	0.78 ± 0.53	0.92
Kt/V (peritoneal)	1.58 ± 0.32	1.39 ± 0.36	0.23

HCO3 was 22.1 ± 1.8 mmol/l, at baseline. At study termination after 24 weeks, pH was 7.36 ± 0.04, and HCO3 21.2 ± 2.3 mmol/l. In the lactate group, pH equaled 7.35 ± 0.12, and HCO3 22.2 ± 1.4 mmol/l at baseline, with the respective values being 7.40 ± 0.03, and 22.3 ± 1.8 mmol/l at the end of the study. There were no statistically significant differences in the presented parameters, within the studied groups or between them.

Urine output has not changed during the study period: after 24 weeks it equaled 910 ml ± 640 ml in the bicarbonate group and 1150 ± 690 ml in the lactate group. Similarly, dialysis ultrafiltration remained stable, as it was 1200 ± 353 ml in the bicarbonate group, and 1220 ± 449 ml in the lactate group, at the end of the study. There were no statistically significant changes in dialysis adequacy, as measured with peritoneal Kt/V, between and within the studied groups. At study termination, peritoneal Kt/V equaled 1.69 ± 0.39 in the bicarbonate group, and 1.49 ± 0.22 in the lactate group. Similarly, renal Kt/V remained stable during the observation period. None of the patients reported inflow abdominal pain in the group with lactate-buffered solution. Whereas only patient from the bicarbonate group experienced inflow pain and reported that it diminished from 2 to 0.

Discussion

In this study we have demonstrated that bicarbonate-buffered peritoneal dialysis solution appears to be similar to standard fluid in terms of the impact on residual renal function and ultrafiltration, as well as on the acid-base balance and the PD fluid inflow pain.

Biocompatibility of fluids used for PD has been a topic of intense studies since the very beginning of PD as a method of RRT [4]. The major factors responsible for the relatively low compatibility of available solutions included: low fluid pH, the use of glucose as an osmotic agent and the addition of lactates as a source of endogenously generated bicarbonates. Low fluid pH was necessary, since at physiologic pH the GDPs are formed due to non-enzymatic glucose disintegration during the process of fluid sterilization. Glucose itself, and in particular GDPs, contribute to protein glycation which leads to formation of advanced glycation end-products (AGE) [1]. These are thought to be responsible for the irreversible damage of the peritoneal membrane that results in ultrafiltration failure and the necessity to treat the patient with hemodialysis.

Currently, the issue of low pH was overcome with the use of two-compartmental fluids, in which glucose

is stored and sterilized in one compartment at a very low pH (2.8-3.1), while the other compartment contains alkaline lactate solution. The solutions from the two compartments are mixed immediately prior to dialysis exchange to form a ready-to-use neutral fluid. However, the use of a lactate buffer is associated with the risk of insufficient correction of metabolic acidosis, as well as with the risk of provoking abdominal pain during the fluid inflow [5-6]. The effects of increased lactate load are associated with a decrease in cellular redox state, thus impairing numerous vital cellular functions [7].

Bicarbonate-buffered dialysis fluids constitute the next step in the quest to obtain an 'ideal' biocompatible solution. Actually, studies on bicarbonates as buffers for dialysis fluids started as early as in the 1960s [8]. However, precipitation of calcium and magnesium carbonate has hindered the use of such solutions. As a result, lactate was utilized as a buffer for many years and was regarded as more stable, with no apparent side-effects. Probably, the first studies with bicarbonate-buffered fluids in two-chamber dialysis sets were performed by Feriani et al. [4]. One chamber contained calcium and magnesium, while the other bicarbonates, to avoid the abovementioned precipitation. The studies that followed, confirmed appropriate correction of metabolic acidosis with bicarbonate-based fluids [5-6]. Additionally, a study by Mactier et al. demonstrated better tolerance of such solutions, as compared to lactate buffered ones, with less abdominal pain during fluid inflow [6].

Better correction of metabolic acidosis was associated with an increase in nPCR, suggestive of improved nutrition [7]. The importance of adequate acidosis correction was highlighted in a Korean study in which decreased serum bicarbonates levels turned out as an independent risk factor for mortality in PD patients [9]. Studies on bicarbonate solutions, performed ex vivo demonstrated improved viability of peritoneal mesothelial cells, and decreased concentrations of factors associated with peritoneal fibrosis and neovascularization (as compared to lactate) [10]. Longitudinal evaluations demonstrated less inflammatory cytokines in dialysis effluents of patients treated with bicarbonate-based solutions, as well as decreased amounts of pro-fibrotic factors and chemokines [11]. Increased concentrations of CA125 in dialysis effluents was also suggestive of high mesothelial mass, in comparison to effluents from lactate-based fluids [12]. These indices of decreased peritoneal injury translated into improved preservation of ultrafiltration capacity in long-term observations [2,13].

Better preservation of peritoneal membrane with bicarbonate-based solutions is also thought to be responsible for decreased incidence of peritoneal infections, reported by some authors [14]. In the present study there were no episodes of dialysis-associated peritonitis in either of the groups. However, the observation was limited to 24 weeks. To evaluate the potential impact of bicarbonate-based fluids on the risk of infections and on the membrane function, longer follow-ups are certainly needed.

Conclusion

International guidelines advocate the use of bicarbonate buffered solutions for peritoneal dialysis. Recommendations for adults (issued by the International Society for Peritoneal Dialysis) and for children (European Pediatric Dialysis Working Group) are especially strong for patients with acute kidney injury [15-16]. However, despite these guidelines and national registration, these fluids have not been used in Poland so far. This study might serve as a contribution to our understanding and experience with bicarbonate buffered solutions in the treatment of PD patients. It confirmed that such fluids are safe, well-tolerated, and do not impair the indices of dialysis adequacy. The study limitations include small sample size and a relatively short observation time of 24 weeks. Given their higher price, long-term studies with large patient groups are needed to further verify the longitudinal advantages of these biocompatible solutions in peritoneal dialysis patients.

Disclosures

In the years 2007-2019 DBO, PJ, MLN were employed by Fresenius NephroCare.

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RESEARCH ARTICLE

Assessment of nutritional status of patients with cancer who are qualified for home enteral nutrition – a retrospective analysis

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Abstract

Introduction: Patients with cancer are at risk of malnutrition. The aim of this study was to assess the nutritional status of patients with cancer who are qualified for home enteral nutrition. Secondary aim is to compare the nutritional status of patients with gastric cancer and with esophageal cancer. **Materials and methods:** Retrospective analysis of medical documentation of 84 participants with cancer who were qualified for home enteral nutrition in Nutritional Counseling Center Copernicus in Gdansk in 2009-2015 was performed. Assessment of nutritional status included body mass index, the level of total protein and albumin in blood serum, total lymphocyte count, and the Nutritional Risk Score (NRS) 2002. **Results:** Patients with gastric cancer most often presented albumin deficiency in comparison with patients with esophageal cancer ($p = 0.02$). The low level of total lymphocyte count in 1mm3 of peripheral blood was observed in 47.6% participants. All the patients qualified for home enteral nutrition received at least 3 points in NRS 2002 and most often 5 points (40.4%). **Conclusions:** All patients required nutritional treatment. Notwithstanding, the nutritional status of patients varied. Hypoalbuminemia was observed more often in patients with gastric cancer in comparison with patients with esophageal cancer.

Keywords: home enteral nutrition · cancer · nutritional status · malnutrition

Citation

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Introduction

According to ESPEN, malnutrition is a condition that results from lack or insufficient consumption and absorption of macro- and micronutrients and energy derived from dietary substances. It leads to impairment of physical and mental body functions, decreases the quality of life, increases the costs of treatment and risk of death [1]. Enteral nutrition is carried out using an artificially created access to the alimentary tract (feeding tube) of patients who do not cover > 60% of their need for protein and calories orally for at least one week. The reduction of food intake may be the result of the functional and structural alterations in the upper part of the alimentary tract [2]. A particular kind of nutritional intervention is home enteral nutrition (HEN), indicated for patients with a properly functioning alimentary tract who do not require hospitalization (hence postpyloric feeding in patients with gastric stasis) [3]. It was observed that 75% of people qualified for HEN suffer from malnutrition [4]. The main aims of home enteral nutrition are to improve the nutritional status, shorten hospital stay as well as to improve quality of life [2, 5-6]. The results of a study by Walewska et al. showed that application of HEN improves the parameters of nutritional status such as total lymphocyte count, transferrin and albumin concentration as well as the body mass index (BMI) [2]. According to other trials, HEN reduces the risk of malnutrition and improves the quality of life of patients who underwent esophagostomy [7-8]. An appropriate nutritional treatment is particularly significant in patients with cancer who most often suffer from malnutrition and cachexia [9]. Malnutrition is mainly observed in patients with pancreatic, gastric, esophageal, head as well as neck cancer [10]. It is estimated that 4-23% of patients die from cachexia [11]. With the use of NRS 2002 system, Sznajder et al. demonstrated that malnutrition occurs in case of 30% of patients who are admitted to a clinical oncology ward [11]. Similar results were obtained by Planas et al. who observed that upon admission to the hospital, 34% of cancer patients (various types of cancer, e.g. head, neck, pancreatic, hepatic) suffer from malnutrition, whereas at the moment of charge from the hospital, this number increases to 36% [12]. According to the another study, malnutrition is observed 52% patients with upper alimentary tract cancer [13]. The differences between the results of the above-cited studies seem to suggest that the higher the cancer is located in the alimentary tract, the faster and more frequently the protein-calorie malnutrition develops [14]. The causes of malnutrition include loss of appetite and eating disorders that are due to chronic inflammation and pain during swallowing caused by tumor growth. In case of people who suffer from alimentary tract cancers (e.g. who underwent gastric or bowel resection), malnutrition may also be caused by impaired nutrient absorption [15]. However, cancer cachexia is more complex phenomenon. Several pathomechanisms are involved in the development of cancer cachexia and cytokines/cachectic factors such as TNF-α, IL-1, IL-6, INF, STAT3 have an important part [16-17].

According to the ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines, the nutritional status of patients with cancer receiving home enteral nutrition should be evaluated during the qualification for HEN with the use of anthropometric measurements (BMI and potentially body composition analysis), laboratory tests (total serum protein, albumin, prealbumin and transferrin concentration, total lymphocyte count) as well as with the use of tool, e.g. NRS 2002 (Nutritional Risk Score 2002), SGA (Subjective Global Assessment) or MUST (Malnutrition Universal Screening Tool) [5, 18-20].

The primary aim of this study is to assess the nutritional status of patients with gastric and esophageal cancer who are qualified for home enteral nutrition. An additional aim is to compare the nutritional status of patients with gastric and esophageal cancer.

Materials and methods

This is a retrospective analysis of medical documentation of patients with cancer who were qualified by the staff of the Nutrition Counseling Center Copernicus (Gdańsk, Poland) for home enteral nutrition in the years 2009-2015. The inclusion criteria: age ≥ 18 years of age, feeding tube, qualification for HEN and diagnosed cancer. The exclusion criteria were as follows: < 18 years of age, lack of feeding tube, diagnosed non-cancer disease, incomplete data. A flow diagram of the participants is presented on the Figure 1.

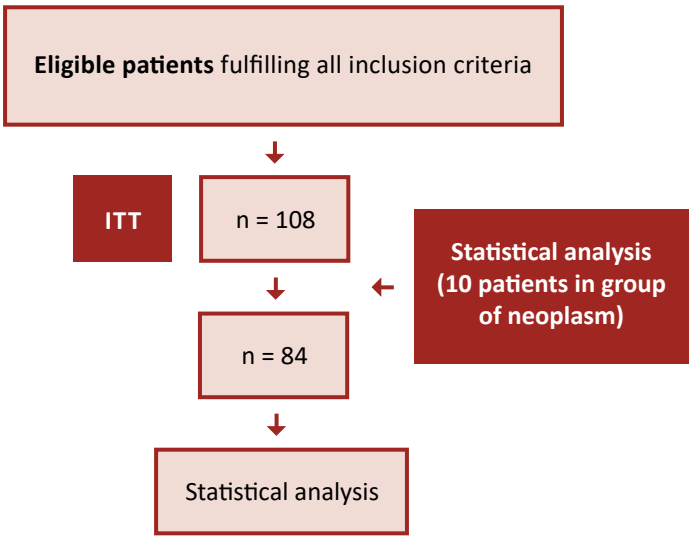


Figure 1. Participants flow diagram

The nutritional status was assessed using the BMI, level of total serum protein, albumin and the total lymphocyte count. The anthropometric and laboratory parameters as well as NRS 2002 tool were carried as part of the home enteral nutrition qualification procedure.

The patients were divided according to the type of cancer they were diagnosed with. All variables analyzed in this study were quantitative. The descriptive statistics were carried out with the use of averages, medians, standard deviations, maximum and minimum values. Only the groups of ≥ 10 patients were selected for the analysis carried out with statistical tests. The remaining patients were excluded due to insufficient number and disproportion in comparison with the statistically-tested groups. The Shapiro-Wilk test was applied to check the normality of distribution of populations subject to research. The Brown-Forsythe test was applied in order to check the homogeneity of variations of the groups compared.

Depending on the data, we used either the U Mann-Whitney test (in case of groups where there are associated ranks), Z score (to find the test probability) or the Student's t-test (to estimate independent variance). In all cases, statistical significance was set at 0.05 and two-tailed test comparison values were calculated on the basis of an assumed null hypotheses regarding lack of differences between respective averages, variances and distributions compared. The calculations were carried out using the Statistica software, version 13.1 (Dell Inc., USA).

Results

The characteristics of study participants are presented in Table 1. After the inclusion and exclusion criteria were applied, 84 patients with gastric and esophageal cancer in the range of 48-93 years of age (median = 68 years of age) were considered. Assessment of patients with gastric cancer (53.6%) and esophageal cancer (46.4%) was distinguished. The characteristics of patients who qualified for analysis are shown in Table 2.

The most frequently used feeding tube was jejunostomy (54.8%) and microjejunostomy (29.8%). In case of patients with gastric cancer, the jejunostomy (64.4%) was the most frequently applied. In case of patients with esophageal cancer the jejunostomy (43.6%) and microjejunostomy (30.8%) were the most frequently applied feeding tubes.

The average value of BMI in all patients was 20.9±3.6 (median of 20.9 kg/m², min. value of 13.2 kg/m², max. value of 29 kg/m²). Among all participants, the largest groups were patients with normal BMI (48.8%, defined as 18.5-25 kg/m²) and underweight (32.2%, BMI < 18.5 kg/m²). Participants with gastric cancer most often presented normal BMI (48.9%) and underweight (26.7%). In case of people with esophageal cancer, normal BMI (48.7%) and underweight (38.5%) were observed. No statistical difference was found between patients with

Table 1. Characteristisc of all participants

Patients (n = 108)	
Age (years)	
Range	36-93
Average	66.8 ± 10.6
Median	67
Diagnosis (%)	
Gastric cancer	41.7
Esophageal cancer	37
Throat cancer	7.4
Laryngeal cancer	3.7
Pancreatic cancer	2.8
Tongue cancer	2.8
Breast cancer	1.9
Colorectal cancer	0.9
Palate cancer	0.9
Prostate cancer	0.9
Artificial access to the alimentary tract (%)	
Nasogastric tube	3.7
PEG	12
Gastrostomy	7.5
Microjejunostomy	25.9
Jejunostomy	50.9

Table 2. Characteristics of participants with gastric and esophageal cancer

Patients (n = 84)	
Age (years)	
Range	48-93
Average	68 ± 10.1
Median	68
Diagnosis (%)	
Gastric cancer	53.6
Esophageal cancer	46.4
Artificial access to the alimentary tract (%)	
Nasogastric tube	2.4
PEG	9.4
Gastrostomy	3.6
Microjejunostomy	29.8
Jejunostomy	54.8

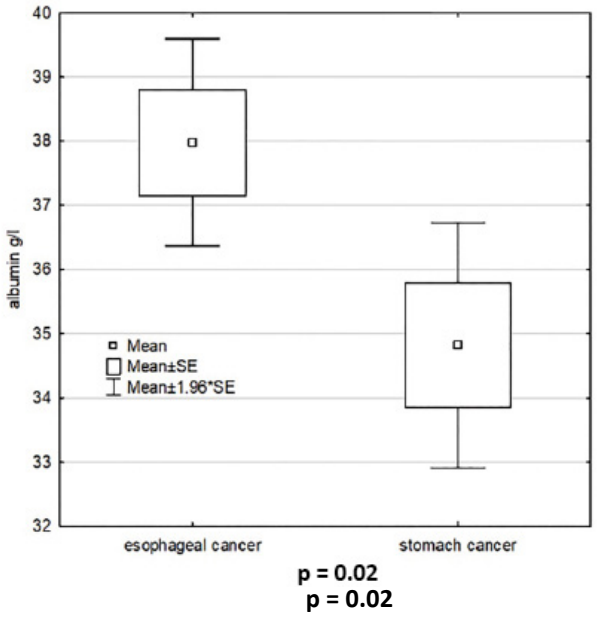
Table 3. Characteristics of patients with gastric and esophageal cancer regarding total serum protein (g/l) and serum albumin (g/l) levels

Laboratory parameters	All participants (%)	Gastric cancer (%)	Esophageal cancer (%)	P
Total protein (g/l)	**n = 84**	**n = 45**	**n = 39**	
< 60	23.8	35.6	10.3	0.24
60-80	71.4	57.7	87.2	
> 80	4.8	6.7	2.5	
Albumin (g/l)	**n = 84**	**n = 45**	**n = 39**	
< 25	2.4	4.4	0	0.02
25-30	11.9	17.8	5.1	
30-35	26.2	31.1	20.5	
> 35	59.5	46.7	74.4	

gastric and esophageal cancer regarding BMI the (p = 0.18). Regarding the ESPEN guidelines about patients > 70 years of age, it was noted that 26.2% of those patients have BMI < 22 kg/m².

The data obtained regarding the total serum protein and albumin level was shown in Table 3. Majority of participants had normal total serum protein (71.4%) and albumin (59.5%) levels. Patients with gastric cancer more often presented protein deficiency in comparison to patients with esophageal cancer, however this was not a statistically significant difference (p = 0.24). The deficiency of albumin was observed more frequently in patients with gastric cancer and this difference was statistically significant (p = 0.02; Graph 1).

The normal level of total lymphocyte count in (> 1500 in 1 mm³) was noted in 52.4% of patients with gastric and esophageal cancer (table 4). Analysis of this parameter did not show a statistically significant difference between patients with gastric and esophageal cancer (p = 0.94).



Graph 1. The comparison of albumin level in patients with esophageal and gastric cancer

Table 4. Characteristics of patients with gastric and esophageal cancer regarding the total lymphocyte count

Total lymphocyte count in 1mm³ of peripheral blood	All participants (%)	Gastric cancer (%)	Esophageal cancer (%)	P
	n = 84	n = 45	n = 39	
> 1500	52.4	51.1	53.9	0.94
1500-1200	15.5	24.3	5.1	
800-1200	17.8	13.3	23	
< 800	14.3	11.1	18	

Among all participants, the largest group constituted patients who received 5 points in NRS 2002 tool (40.4%). Patients with gastric cancer most often received 5 points, while patients with esophageal cancer - 4 points (Table 5). It was not a statistically significant difference (p = 0.53).

Discussion

There is a lack of data from Poland about the nutritional status of gastric and esophageal cancer patients qualified for HEN. Furthermore, there are not many studies regarding the nutritional status of patients treated using HEN. One of the limitations of our study is non-homogenous population. Moreover, this study did not include the stage of disease. The results may be different if patients with the same type of neoplasm are assessed.

Among the anthropometric measurements used in the assessment of nutritional status, BMI deserves attention. Our results were similar to those obtained by Walewska et al., who noted that BMI at the start of HEN was 19.4 ± 4.3 kg/m2 [2]. In our study we showed that malnutrition assessed on the basis of BMI was observed among 32.2% of cancer patients, whereas Bruzgielewicz et al reported 41% [21]. Anthropometric measurement is a cheap and simple method, however such measurements should only be a part of complex assessment of nutritional status. This is particularly true for patients with edema which leads to a significant increase in BMI. The gold standard is body mass composition analysis, which includes lean body mass, fat mass and total body water. In some cases, weight loss may be caused by reduction of lean body mass. According to the GLIM Criteria for diagnosing of Stage 1 or Stage 2 malnutrition only one phenotypic and one etiologic criterion needs to be fulfilled. To assess patients regarding this criteria, unintentional weight loss during last months is necessary; however, it is a retrospective analysis of patients' documentation that do not include this data [22]. Therefore, this is an additional limitation of this study.

Table 5. Characteristics of patients with gastric and esophageal cancer regarding the NRS 2002 system

NRS 2002 (points)	All participants (%)	Gastric cancer (%)	Esophageal cancer (%)	P
	n = 84	n = 45	n = 39	
< 3	0	0	0	0.53
3	3.6	4.4	2.6	
4	31	22.2	41	
5	40.4	51.1	28.2	
6	25	22.3	28.2	
7	0	0	0	

Table 6. Statistical comparison of nutritional parameters of patients with gastric and esophageal cancer

Esophageal cancer (average, standard deviation)		Gastric cancer (average, standard deviation)		P
BMI*				
20.3 ± 3.3		21.4 ± 3.9		0.18
Total serum protein*				
66.8 ± 5.8		64.5 ± 6.5		0.24
Serum albumin*				
38 ± 5.1		34.8 ± 6.5		0.02
Median Esophageal cancer	**Quartile range Esophageal cancer**	**Median Stomach cancer**	**Quartile range Stomach cancer**	**P**
NRS 2002**				
5	2	5	1	0.53
Total lymphocyte count**				
1566	1063.6	1580.6	731.7	0.94

***t Student test (independent variance estimation)**

****U Mann-Whitney Test**

The assessment of nutritional status should include laboratory tests that may be divided into biochemical (level of total protein, albumin, prealbumin and transferrin in blood serum) and immunological (total lymphocyte count) [7, 10, 13]. Similar results to ours were noted in a study by Walewska et al., where the average albumin concentration was 3.46 g/l, which indicates low malnutrition at the moment of initiation of home enteral nutrition [2]. According to Szczepanik et al., deficiency of albumin was observed in case of 17% patients who suffer from alimentary tract cancer [23]. According to own research, albumin deficiency most often occurred in patients with gastric cancer in comparison with patients with esophageal cancer. The level of serum albumin directly reflects the nutritional status of a patient. Their level is affected not only by supply of protein in diet, but also by the presence of inflammation and level of body hydration. However, albumins are proteins with long half-life period of 21 days, therefore they are not used to determine very fast changes that occur during nutritional therapy [10]. It is noteworthy that laboratory parameters are only complementary with other methods of nutritional status assessment of patients with gastric as well as esophageal cancer.

Regarding the total lymphocyte count, our results were similar to those presented by Walewska et al. study; the average total lymphocyte count at the moment of initiation of HEN was 1906/mm3, so it was normal [2]. In turn, the symptoms of malnutrition on an insignificant, moderate or severe level were observed in 34.3% of patients. Comparable results were also obtained in Szczepanik et al. trial, where the deficiency of total lymphocyte count was observed in 42.3% of patients with alimentary tract cancer [23]. According to the Bruzgielewicz et al. study, the low level of total lymphocyte count was observed in 37% of patients with laryngeal and lower throat cancer [21]. Lower level of lymphocytes is a result of lower synthesis and immunosuppression related to malnutrition. An additional limitation of our study is that we did not assess the role of lymphocytes in nutritional status because the subpopulations of T cells were not included in the methodology.

Complex assessment of nutritional status should cover standardized tool such as NRS, SGA or MUST [1]. It is known that PG-SGA (Patient Generated Subjective Global Assessment) method is one of the best to assess nutritional status, because it includes among other edemas, unintentional weight loss during last 6 months and even 2 weeks, alterations in food intake [24]. Moreover, the SGA tool is more appropriate to assess the nutritional status mainly of patients with cancer in which the malnutrition may be develop in

short period [20]. The patient documentation available for our analysis contained only the NRS 2002 scores, thus it is another limitation of this study. Among all patients, the largest group was patients who received 5 points (40.5%). All patients qualified for HEN received ≥ 3 points in NRS 2002, which indicates a need for nutritional treatment.

The limitations of our retrospective study present the lack of appropriate assessment of nutritional status of patients with cancer in clinical practice in Poland. The body composition analysis should be performed and the unintentional weight loss during last months should be noted, therefore the role of clinical nutritionist should also be taken into consideration.

Conclusions

The assessment of patients' nutritional status during qualification for home enteral nutrition is required to identify patients at risk of malnutrition or malnourished. It is necessary to introduce an appropriate nutritional treatment and prevent the consequence of malnutrition. In the present study, the nutritional status of patients qualified for HEN varied. Most patients were characterized by normal BMI, normal total serum protein and albumin level as well as normal total lymphocyte count. Hypoalbuminemia was observed more often in patients with gastric cancer in comparison with patients with esophageal cancer. All patients required nutritional treatment.

The authors have no conflicts of interest to declare.

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RESEARCH ARTICLE

Risk factors of acute respiratory distress syndrome after on-pump cardiac surgery in the INFLACOR cohort study

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is a serious complication after cardiac surgery with a variety of clinical risk factors. It was hypothesized that genome variants predispose these patients to it. **Material and methods:** A cohort of 509 adult Caucasians undergoing on-pump cardiac surgery were observed for postoperative ARDS defined by the Berlin definition. Clinical variables and 10 single-nucleotide variants of genes involved in inflammatory pathways were analyzed for associations with four groups, defined by paO2/fiO2 (PF) ratio: 1) no ARDS (PF > 300 mmHg), 2) mild ARDS (200 < PF ≤ 300 mm Hg), 3) moderate ARDS (100 < PF ≤ 200 mm Hg), and 4) severe ARDS (PF ≤ 100 mmHg). Variables remaining in trends at $p < 0.05$ were considered significant. **Results:** The prevalence of ARDS was 7.9%. Only *LBP* rs2232582 remained in a genotypic trend with ARDS aggravation ($p = 0.08$). Clinical variables associated with ARDS aggravation: impaired left ventricular ejection fraction ($p = 0.04$), pulmonary hypertension ($p = 0.01$), intraoperative hypotension ($p = 0.009$), and postoperative day 1 white blood cell count ($p = 0.015$). More aggravated ARDS was associated with longer mechanical ventilation ($p=0.01$) and length of stay in ICU ($p = 0.002$). **Conclusions:** The borderline association with *LBP* rs2232582 and the identified risk factors suggest possible involvement of the LPS-LBP pathway in ARDS of the INFLACOR cohort.

Keywords: cardiac surgery · acute respiratory distress syndrome · cardiopulmonary bypass · *LBP* rs2232582

Citation

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Introduction

Early postoperative morbidity after open-chest cardiac surgery is responsible for prolonged hospital stay, increased treatment costs and higher early mortality [1-5]. Postoperative respiratory failure (PRF) is considered one of the most important early postoperative complications after cardiac surgery [6].

In non-cardiac surgical patients, PRF defined as acute respiratory distress syndrome (ARDS) is most commonly associated with infection [7-8]. Whereas in cardiac surgical patients, inflammatory reactions triggered by the release of non-infectious antigens due to intraoperative gut and lung hypoperfusion during cardiopulmonary bypass (CPB), cell injury, blood contact with artificial surfaces, and blood product transfusion-related immune reactions are considered as the major pathological pathways which lead through massive cytokine release to postoperative ARDS and other organ dysfunction [9-11]. Mortality risk prediction models used in cardiac surgery, such as the EuroSCORE II model, were also shown to be effective in predicting specific postoperative morbidities, e.g. acure kidney injury (AKI) and PRF [12-13].

In addition to the identified clinical risk factors for postoperative morbidity, genome variants were considered to be useful in the prediction of specific postoperative complications after cardiac surgery [14-16]. Genetic association studies in cardiac surgical cohorts reported that single-nucleotide variants (SNVs) of the interleukin 6 (IL6), intercellular adhesion molecule 1 (ICAM1), E-selectin (SELE), C-reactive protein (CRP), and lipopolysaccharide binding protein (LBP) genes were associated with perioperative myocardial infarction (MI), AKI, bleeding, or cognitive impairment after coronary artery bypass graft surgery [17-21]. Other complications, such as bacteremia, AKI, and ARDS, were reported to be associated with SNVs of nucleotide-binding oligomerization domain-containing protein 2 (NOD2), toll-like receptor 4 (TLR4), mannose-binding protein-associated serine protease 2 (MASP2), nitric oxide synthase 3 (NOS3), and tumor necrosis factor (TNF) genes in non-cardiac surgical intensive care unit (ICU) patients [22-24].

The aim of this study was to test the hypothesis that selected SNVs of genes activated during the inflammatory response in humans may be associated with postoperative ARDS after on-pump cardiac surgery.

Material and methods

The prospective observational genetic association study INFLACOR (INFLammation After Cardiac OpeRation) was designed and conducted to evaluate the risk factors for 8 postoperative complications in patients undergoing open-heart cardiac surgery on cardiopulmonary bypass. The clinical variables, 4 selected cytokines and 10 SNVs were compared between patient groups. Adult Caucasian patients scheduled for open-heart surgery between October 22, 2009, and March 16, 2011, who signed informed consent were included. Patients scheduled for off-pump procedures, those with previous open-chest cardiac surgery and those who underwent emergency operations were excluded. The study protocol was approved by local Bioethics Commission (NKEBN/358/2007).

The primary outcome measure was a genotypic association between any of the selected SNVs and ARDS. The ten candidate SNVs were selected from previously published genotype-phenotype associations using the candidate gene approach: *IL6* – rs1800796, *LBP* – rs2232582, *ICAM1* – rs5498, *CRP* – rs1800947, *NOD2* – rs2066844, *TNF* – rs1800629, *MASP2* – rs2273346, *SELE* – rs1805193, *NOS3* – rs1799983, *TLR4* – rs4986790. The detailed genotyping method was published elsewhere [3]. ARDS was diagnosed following the so-called "Berlin definition" as the presence of bilateral lung infiltrates on chest X-ray (CXR) within 48 hours after operation combined with a mean paO_2/fiO_2 ratio (PF) ≤ 300 mm Hg on mechanical ventilation and in absence of cardiogenic pulmonary edema [25]. The mean PF was calculated from all blood gas measurements performed on mechanical ventilation during the first postoperative day. Patients were assigned to one of four groups of disease severity according to the level of hypoxaemia: 1) no ARDS (PF > 300 mmHg), 2) mild ARDS (200 < PF ≤ 300 mm Hg), 3) moderate ARDS (100 < PF ≤ 200 mmHg), and 4) severe ARDS (PF ≤ 100 mmHg). Secondary outcome measures included associations between 43 clinical candidate variables, including 17 pre-, 19 intra-, and 7 post-operative variables (Tables S1, S2, and S3 in the Supplementary Materials). Levels of interleukin 6 (IL-6), intercellular adhesion molecule 1 (ICAM1) and soluble E-selectin (sESEL) were measured in samples obtained three hours after admission to the postoperative ICU, centrifuged and cooled immediately, and stored in deep-freeze until being assayed with bead-based flow cytometry. The detailed processing protocol is published elsewhere [3]. Outcome data included total hours on ventilator (HOV), length of stay in ICU (LOS-ICU) and hospital (LOS-HOS), as well as 30-day and 5-year survival.

Statistical methods

The original cohort size calculations were based on the Kelsey formula with assumptions of 80% of power, 95% two-sided confidence interval, and at SNP's exaggerating an effect with an odds ratio (OR) of at least 1.65. The n = 492 was rounded up to n = 525 for eventual loss of cases during the study. Genotypic association

with the genotyped SNV was recognized by chi-square test for trend, when the wild-type and heterozygotic genotypes were correlated in a trend with ARDS severity, with a $p \leq 0.05$. Univariate analysis was used to identify the clinical risk factors for ARDS. Associations between continuous data were evaluated by either analysis of variance (ANOVA; A) or the Kruskal-Wallis (KW) test, depending on the data variance in Bartlett's test. Reported values for ANOVA or the KW tests are the mean and standard deviation (SD) or the median and interquartile range (IQR), respectively. Trends in the candidate variables between the ARDS groups with $p < 0.05$ were considered significant. Epi-Info 7 (CDC, Atlanta, GA, USA; free license) and Statistica 12 (Statsoft, Tulsa, OK, USA) software were used for the analyses.

Results

Clinical data, genotyping, and cytokine measurements were obtained from n = 525 patients. Of them, n = 509 (97.0%) were included in the analyses. The patient flow and reasons for exclusion from analysis are presented in Figure 1.

Among the analyzed n = 509 patients, n = 40 (7.9%) met the criteria for ARDS according to the Berlin definition. Lung parenchyma infiltrates on CXR were identified in n = 73 (14.3%) patients. Sustained hypoxemia, defined by a mean PF≤300 mm Hg on mechanical ventilation, was diagnosed in n = 301 (59.1%) patients. Simultaneous CXR lung opacities and hypoxemia were present with mild (n = 28, 5.5%), moderate (n = 11, 2.2%) and severe (n = 1, 0.2%) intensity, which corresponded to 70%, 28%, and 2% of the ARDS patients.

Another frequent CXR finding was lung congestion and atelectasis, which were found in n = 143 (28.1%) and n = 12 (2.4%) patients respectively, however neither of them was associated with hypoxemia or ARDS worsening (tests for PF means and prevalence trends with $p > 0.05$).

The primary outcome sought in this analysis was a genotypic association between any of the 10 genotyped SNVs of genes involved in the human inflammatory response and the aggravation of the ARDS phenotype. Only the *LBP* rs2232582 (19983 T > C) suggested a genotypic trend, with a $p = 0.08$. Carriers of the recessive C allele presented with lower risk for ARDS in an additive model. However, none of the tested genetic associations reached the assumed level of significance.

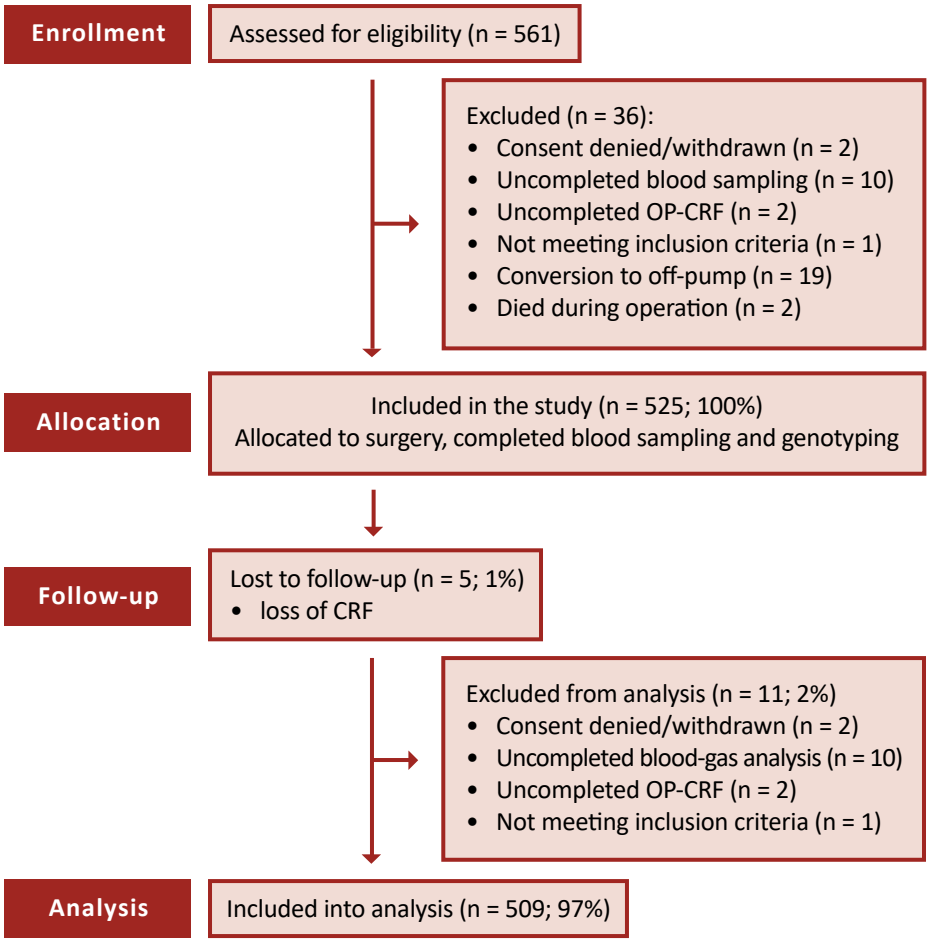


Figure 1. CONSORT flow diagram of the INFLACOR trial and patient qualification for analyses on ARDS

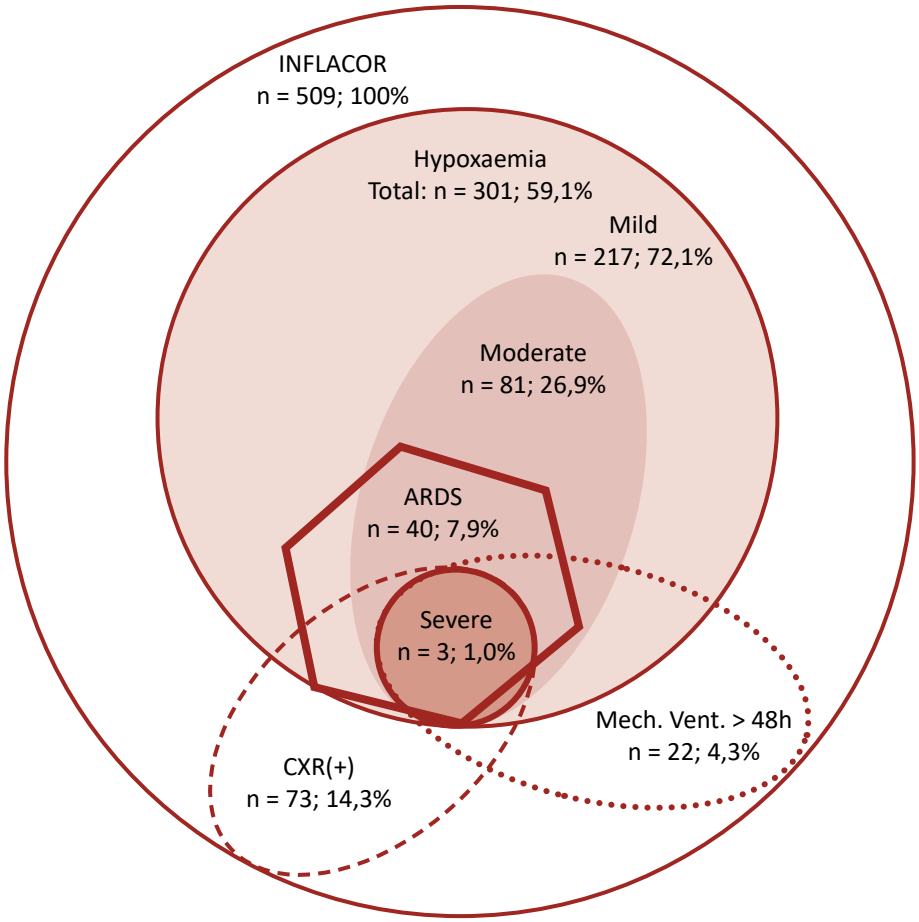


Figure 2. Prevalence of hypoxemia,
pulmonic opacities on chest X-ray, and prolonged mechanical ventilation in n = 509 patients from the INFLACOR study

Forty patients were diagnosed with ARDS upon simultaneous presentation of lung opacities on chest X-ray and sustained hypoxemia defined by pO_2/fiO_2 (PF) ≤ 300 on mechanical ventilation. Of the n = 40 patients with ARDS n = 28 (70%) presented with mild hypoxemia, n = 11 (28%) with moderate hypoxemia, and n = 1 (2%) with severe hypoxemia. Patients with ARDS made up 7.9% (n = 40/509) of the whole analyzed cohort, 13.3% (n = 40/301) of patients with hypoxemia, and 54.8% (n = 40/73) of patients with a positive chest X-ray, but only 16.9% (n = 10/59) of patients ventilated for longer than 24 hours and 13.6% (n = 3/22) of patients ventilated mechanically for longer than 48 hours. The prevalence of hypoxemia, a positive chest X-ray, and mechanical ventilation > 48 hours provided in the graph was calculated for the whole cohort of n = 509 patients. The prevalence of hypoxemia levels (mild, moderate, and severe) is calculated for n = 301 patients with hypoxaemia.

A list of four risk factors was identified from the clinical candidate variables. Of the 17 analyzed pre-operative candidate variables, only impaired left ventricular ejection fraction and pulmonary hypertension were associated, with a significant trend, with ARDS aggravation.

Supplementary Table 1. Analysis of trends between preoperative candidate variables and ARDS aggravation in n = 509 patients from the INFLACOR cohort → go to: https://ejtcm.gumed.edu.pl/files/56

Six categories of surgical procedures were defined based on the type and complexity of the surgery. The prevalence of ARDS did not differ between the surgical groups.

Supplementary Table 2. Analysis of trends between intra-operative candidate variables and ARDS aggravation in n = 509 patients from the INFLACOR cohort → go to: https://ejtcm.gumed.edu.pl/files/57

Of the 14 intraoperative candidate variables, four – dexamethasone dose and number of transfused units of packed red blood cells, fresh frozen plasma and platelets concentrate – were analyzed both as continuous variables and after conversion into categorical variables. Significant correlations with ARDS severity were identified only for the duration of intraoperative hypotension, defined as mean arterial pressure < 60 mmHg.

Of the seven analyzed postoperative variables only the white blood cell (WBC) count showed a si-

Table 1. Analysis of genotypic trends between the single nucleotide variants of 10 genes involved into inflammatory response and ARDS aggravation in n = 509 patients from the INFLACOR cohort

No.	ARDS SNV, Genotypes	(1) n = 469 (92.1%)	(2) n = 28 (5.5%)	(3) n = 11 (2.2%)	(4) n = 1 (0.2%)	p-value for trend
1	*IL6* rs1800796 GG CG CC	420 (89.6) 44 (9.4) 5 (1.1)	23 (82.1) 5 (17.9) 0 (0)	9 (81.8) 2 (18.2) 0 (0)	1 (100) 0 (0) 0 (0)	0.17[1]
2	*LBP* rs2232582 TT CT CC	345 (73.6) 111 (23.7) 13 (2.8)	24 (85.7) 4 (14.3) 0 (0.0)	10 (90.9) 1 (9.1) 0 (0)	1 (100) 0 (0) 0 (0)	0.08[1]
3	*ICAM1* rs5498 AA AG GG	148 (31.6) 237 (50.5) 84 (17.9)	4 (14.3) 18 (64.3) 6 (21.4)	6 (54.6) 4 (36.4) 1 (9.1)	0 (0) 1 (100) 0 (0)	0.63[1], 0.79[2]
4	*CRP* rs1800947 GG GC CC	382 (81.5) 87 (18.6) 0 (0)	23 (82.1) 5 (17.9) (0)	10 (90.9) 1 (9.1) (0)	1 (100) 0 (0) 0 (0)	0.42[1]
5	*NOD2* rs2066844 CC CT TT	437 (93.2) 32 (6.8) 0 (0)	27 (96.4) 1 (3.6) 0 (0)	11 (100) 0 (0) 0 (0)	1 (100) 0 (0) 0 (0)	0.26[1]
6	*TNF* rs1800629 GG GA AA	340 (72.5) 121 (25.8) 8 (1.7)	21 (75.0) 7 (25.0) 0 (0)	8 (72.7) 3 (27.3) 0 (0)	1 (100) 0 (0) 0 (0)	0.82[1]
7	*MASP2* rs2273346 TT CT CC	457 (97.4) 12 (2.6) 0 (0)	27 (96.4) 1 (3.6) 0 (0)	10 (90.9) 1 (9.1) 0 (0)	1 (100) 0 (0) 0 (0)	0.28[1]
8	*SELE* rs1805193 GG GT TT	373 (79.5) 90 (19.2) 6 (1.3)	16 (57.1) 10 (35.7) 2 (7.1)	10 (90.9) 1 (9.1) 0 (0)	1 (100) 0 (0) 0 (0)	0.61[1], 0.28[2]
9	*NOS3* rs1799983 GG GT TT	210 (44.8) 211 (45.0) 48 (10.2)	15 (53.6) 9 (32.1) 4 (14.3)	5 (45.5) 6 (54.6) 0 (0)	1 (100) 0 (0) 0 (0)	0.45[1], 0.47[2]
10	*TLR4* rs4986790 AA GA GG	415 (88.5) 53 (11.3) 1 (0.2)	23 (82.1) 5 (17.9) 0 (0)	10 (90.9) 1 (9.1) 0 (0)	1 (100) 0 (0) 0 (0)	0.76[1]

[1]p-value for X^2 for trend with the heterozygotic (1) or homozygotic recessive (2) genotype treated as risk variable; as none test reached the assumed significance level of $p \leq 0.05$, odds ratios are not provided;

ARDS – acute respiratory distress syndrome; letters: A, C, G, T – denominate respectively adenine, cytosine, guanine, thymine nucleotides in genotyped single nucleotide polymorphisms; CRP – C-reactive protein; ICAM1 – intercellular adhesion molecule 1; IL6 – interleukin 6; LBP – lipopolysaccharide binding protein; MASP2 – mannose-binding protein-associated serine protease 2; NOD2 – nucleotide-binding oligomerization domain-containing protein 2; NOS3 – nitric oxide synthase 3; SELE – E-selectin, TLR4 – toll-like receptor 4; TNF – tumor necrosis factor.

gnificant trend with ARDS severity, though CRP and glucose level were close (both with a p = 0.08).

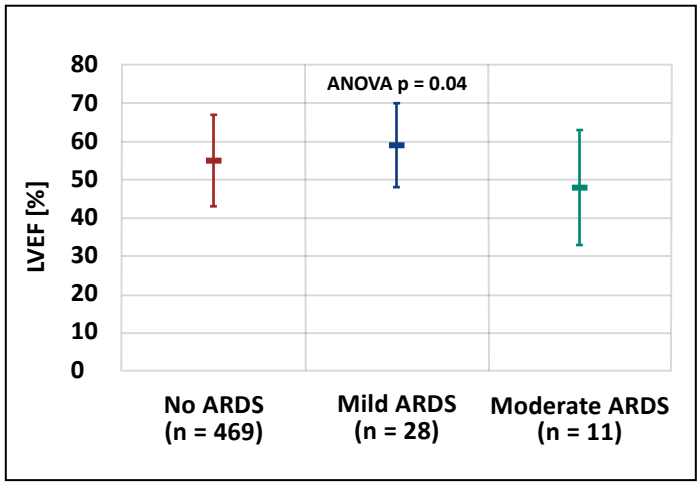
Supplementary Table 3. Analysis of trends between postoperative candidate variables and ARDS aggravation in n = 509 patients from the INFLACOR cohort → go to: https://ejtcm.gumed.edu.pl/files/58

Outcome analysis

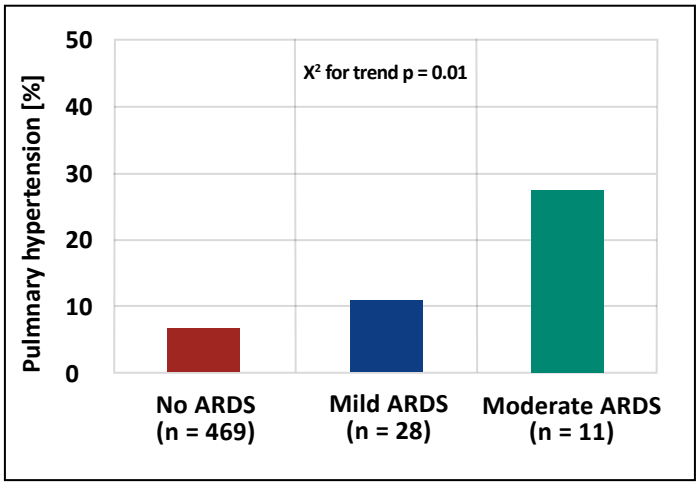
The median time of mechanical ventilation in the whole cohort was 11.9 hours (IQR: 8.5-17.9). Of the total of n = 509 patients, n = 59 (11.6%) and n = 22 (4.3%) were mechanically ventilated longer than 24 and 48 hours, respectively. Of the patients ventilated longer than 24 and 48 hours, ARDS was diagnosed in n = 10/59 (16.9%) and n = 3/22 (13.6%), respectively. Patients with more severe ARDS required more HOV and longer LOS-ICU.

Discussion

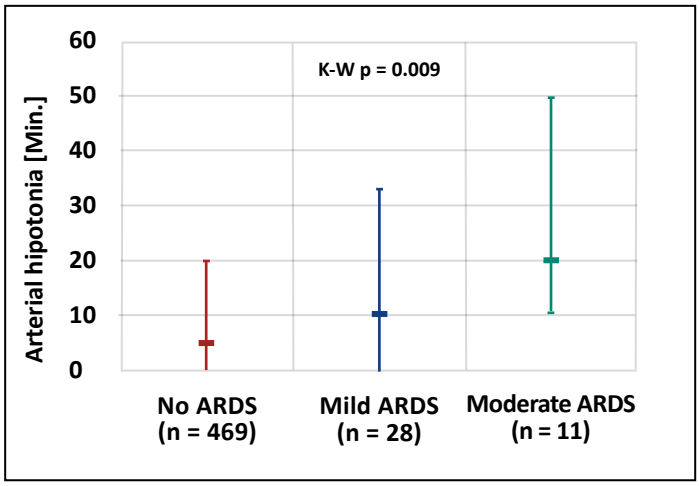
The INFLACOR study was primarily designed as a genetic association study, following projects such as the PEGASUS and FIFA trials [3, 17, 19]. The ability to genotype selected SNVs at the turn of the millennium led to the sound hypothesis that genetic tests could improve our prediction ability of the most devastating complications of on-pump cardiac surgery [15-16, 26]. Crucial for identification of any genetic association is



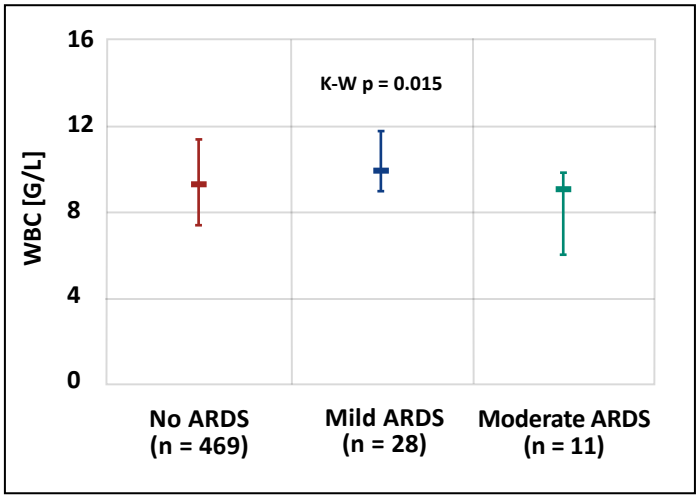
Panel A. Preoperative left ventricular ejection fraction



Panel B. Pulmonary hypertension



Panel C. Intraoperative arterial hypotension (MAP ≤ 60 mmHg)



Panel D. Postoperative day 1 WBC

Figure 3. Perioperative variables associated with ARDS severity in the n = 509 INFLACOR patients: left ventricular ejection fraction (LVEF; Panel A), pulmonary hypertension (Panel B), duration of intraoperative hypotension (Panel C), and postoperative day 1. white blood cell count (WBC; Panel D)

Table 2. Outcome variables and ARDS aggravation in n = 509 patients from the INFLACOR cohort

Outcome	(1) n = 469 (92.3%)	(2) n = 28 (5.5%)	(3) n = 11 (2.2%)	(4) n = 1 (0.2%)	p-value
HOV [hours] (median; IQR)	11.9 (8.5-17.5)	10.3 (7.9-14.8)	19.4 (15.7-21.8)	42.6	**0.01**
LOS-ICU [days] (median; IQR)	1.6 (0.9-2.8)	2.9 (1.0-5.4)	3.0 (1.0-4.8)	2.8	**0.002**
LOS-HOS [days] (median; IQR)	8.0 (7.0-11.0)	9.0 (7.0-13.0)	10.0 (7.0-10.0)	10.0	0.82
30-day mortality [%]	3.0	7.1	9.1	0	0.11
5-year mortality [%]	22.6	32.1	18.2	0	0.67

HOV – hours on ventilator, LOS – length of stay, ICU – intensive care unit, HOS – hospital

the precise definition and selection of the phenotypes used as outcome measures. The correct allocation into the true-positive and true-negative subgroups is the cornerstone of correct statistical results and appropriate clinical inference. In the INFLACOR study, the Berlin definition of ARDS was adopted to define the affected patients [25]. This definition defines the ARDS by the concomitant presence of pulmonary infiltrates on CXR and hypoxemia along with an absence of left ventricle failure. The Berlin definition introduces three, mutually exclusive, severity stages of the syndrome, based upon the severity of hypoxemia [25]. This continuum of disease aggravation was utilized for calculating trends for the analyzed variables in the current study. A significant association trend between a variable and ARDS aggravation was assumed to strengthen the inference over the identified risk factors. This methodology is relatively infrequent and novel in ARDS studies in cardiac surgical patients but is compatible with the recommendations from the Berlin conference on ARDS [25].

The primary outcome in this study was any genotypic association with ARDS. None of the ten tested SNVs breached the assumed significance level of a trend with ARDS severity. However, the carriers of the wild-type (T) allele in *LBP* rs2232582 presented a genotypic trend towards a higher incidence of more aggravated ARDS at a $p = 0.08$. This novel finding requires confirmation on a larger sample. The *LBP* rs2232582 was previously reported to be associated with postoperative MI, also with T being the risk allele [17]. The protein encoded by the *LBP* gene, the lipopolysaccharide binding protein (LBP), is involved in the acute-phase immunologic response to gram-negative bacterial infections. Gram-negative bacteria contain a glycolipid, lipopolysaccharide (LPS), on their outer cell wall. Together with bactericidal permeability-increasing protein, LBP binds LPS and interacts with the CD14 receptor, probably playing a role in regulating LPS-dependent monocyte responses. LPS from Gram-negative bacteria have been shown to trigger experimental ARDS in an animal model [27]. The serum level of LBP has been associated with survival in patients with ARDS and sepsis [28]. Furthermore, the *LBP* rs2232582 is reported to have a significant association with highly active antiretroviral-associated lipodystrophy syndrome, progressively higher bacterial translocation, serum LPS, and LBP level [29]. LPS may translocate from the patient gut microbiota during prolonged hypothermia and/or gut hypoperfusion on CPB [9].

Shock was reported to be a risk factor for ARDS after cardiac surgery by Milot et al., which is consistent with prolonged intraoperative hypotension, the sole intraoperative risk factor in our study [30]. Inflammation was an important contributor to ARDS in the INFLACOR patients, as displayed by postoperative day 1 increase in WBC, CRP and glucose levels.

Hence, the role of the LPS-LBP inflammatory pathway seems to be a probable dominant pathway of ARDS in the INFLACOR cohort. Thus, a pivotal role for *LBP* rs2232582 in the pathogenesis of ARDS seems possible and probable. Unfortunately, the INFLACOR patients were not tested neither for LPS, nor for the LBP levels in serum.

Despite the lack of significant genetic associations, this study identified four clinical risk factors of ARDS using the trend analysis. A recent review of clinical studies on ARDS in cardiac surgical patients revealed a great variability of clinical risk factors [31]. While some studies identified massive transfusion as a risk factors of TRALI-ARDS (a risk factor not confirmed in the present study), other studies reported impaired left ventricular ejection fraction and/or pulmonary hypertension [31-33]. Both were found to be risk factors also in the INFLACOR study.

In cardiac surgical cohorts, it is common to utilize only the duration of mechanical ventilation to define PRF [1, 6, 13, 34]. The rates of mechanical ventilation > 24 hours of 11,3% observed in this study were similar to those in other cardiac surgical studies [4, 32-33]. The prevalence of ARDS among patients ventilated for longer than 24 hours of 16.9% and among patients ventilated for longer than 48 hours was 13.6%, which may appear low. However, an epidemiological study by Rubenfeld in a cohort of 4251 non-cardiac surgical patients ventilated for longer than 24 hour diagnosed ARDS in only 26.2% [35]. Notably, interobserver variability in the interpretation of CXR with regard to ARDS diagnosis has been emphasized an important bias [36--37]. This factor might have also influenced the discrepancy between CXR(+)-patients and ARDS-patients in the current analyses. Furthermore, it was differentiated between pulmonary congestion and lung opacities. However, a systematic differentiation between cardiogenic lung edema and ARDS was not performed. Part of the analyzed cases presented with pulmonary hypertension and impaired LVEF, thus making a cardiogenic component of the ARDS even more probable. Unfortunately, the detailed data of postoperative echocardiographic examination or pulmonary artery wedge pressure, which would allow to discriminate the two conditions, were not recorded in the study.

ARDS resulted not only in longer mechanical ventilation but also in prolonged ICU stay. However, the whole stay in the surgical department did not differ between patients with and without ARDS, as well as 30-day and 5-year mortality were also not affected. This might be the result of analyzing data only until discharge from the cardiac surgical department and not until final hospital discharge.

This study failed to confirm a statistically significant association between the ARDS phenotype and selected SNVs due to the low incidence of ARDS in the relatively small analyzed cohort. Another important limitation of our study was the lack of systematic verification of CXR interpretations for bilateral opacities. The selection of mean PF on mechanical ventilation as the measure of ARDS severity, instead of the minimal PF, maximal PF, or first-day trends in the PF, may be disputable, but the average value was considered the most reliable parameter of sustained hypoxaemia. Another important limitation is the lack of systematic discrimination between cardiogenic pulmonary edema and ARDS. Finally, the lack of a replicative cohort is an important disadvantage of the present study, however its protocol was designed before the recommendations on genetic association studies were published [38].

Conclusions

The prevalence of ARDS among the adult patients undergoing cardiac surgery on cardiopulmonary bypass was 7.9%. Identified clinical risk factors were: impaired left ventricular ejection fraction, pulmonary hypertension, intraoperative hypotension, and postoperative day 1 white blood cell count. A probable genotypic trend for *LBP* rs2232582 suggests that the role of the LPS-LBP inflammatory pathway might have played a dominant role in the pathogenesis of ARDS in the INFLACOR cohort.

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RESEARCH ARTICLE

Anthropometric measurements, nutritional status and body composition in children with cystic fibrosis – the prospective study

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Abstract

Background: Cystic fibrosis(CF),despite much progress in therapy, remains the disease which affects nutrition. Nutrition is an important prognostic factor of the outcome of the disease. We want to evaluate physical development, nutrition and body composition in CF children. **Material and methods:** 75 children diagnosed with CF (9 months to 18 years old) were included into the study. 33 healthy children (9 months to 18 years old) constituted the control group. The study consisted of 2 stages. In the first the differences between groups were investigated. The second, took place a year later. At each time point the following measurements were performed: height, body mass, skin fold, arm circumference; BMI, FFM%, FM% and Frisancho index. FFM (fat free mass), FM (fat mass), muscle mass, TBW (total body water) were evaluated by mans of BIA(bioimpedance). **Results:** CF children were shorter than healthy children. Stunting affected 18,67% of CF patients at first examination and 21,6% a year later. Underweight was diagnosed in 28% of patients at the beginning and in 41.2% a year after. Underweight was the result of both little FM and scarce muscle mass. **Conclusions:** Many children with cystic fibrosis suffers from short stature and underweight, which progresses within time. FFM decreases with the disease progress

Keywords: nutritional status · cystic fibrosis · bioimpedance · physical development · fat free mass

Citation

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Introduction

Cystic fibrosis (CF) is caused by mutation of the chloride channel CFTR (Cystic fibrosis transmembrane conductance regulator) gene. This mutation is responsible for morphological changes which result in the accumulation of secretions in the external ducts and subsequent malfunction of exocrine organs of the digestive and respiratory system [1]. Patients with CF are prone to malnutrition due to malabsorption and increased energy expenditure.

Treatment of CF is complex and should be interdisciplinary as it involves the pulmonary disease and its complications, pancreatic enzyme supplementation, nutritional treatment and physical therapy. Nutritional status is one of the prognostic factors of disease outcome [1]. It is well-known that during the course of cystic fibrosis unfavourable changes in body composition take place. One of them is depletion of muscle mass, which results in impairment of lung function, aggravated coughing and worse results in spirometry. That is why we aimed to evaluate prospectively assess anthropometric parameters and body composition in children suffering from cystic fibrosis.

Methods

Our study included 75 children with cystic fibrosis (33 girls and 42 boys) who were 9 months to 18 years of age (mean 8,7 years ± 5,3). Nine of them (4 girls, 5 boys) were < 2 years old, 14 patients (5 girls, 9 boys) were 2-5 years old, 35 (15 girls, 20 boys) were 6-14 years old and 17 patients (9 girls, 8 boys) were > 15years old. The 23 patients (30,6%) were diagnosed via neonatal screening. The CF diagnosis was confirmed via molecular examination of the CFTR gene. based Pancreatic exocrine insufficiency was diagnosed via stool elastase-1 activity in 65 patients (86,7%). None of the patients underwent nutritional intervention. All of the CF patients had oral nutrition in accordance with the applicable pediatric CF recommendations [2].

Lung function (FEV_1, FVC and FEF_{25-75}) was assessed using a MES Lungtest 1000 spirometer (Kraków, Poland), calibrated according to the manufacturer's instructions. All of the study participants were in stable condition without respiratory exacerbation within the last 4 weeks and without signs of oedema or dehydration.

We conducted a two-step prospective study. Measurements were performed on the day of enrolment into the study and 12 months later. The number of patients in both stages of the study varied due to resignation from participation (several patients), absence on the follow-up visit and death (1 patient). At both time points, the patients were assessed using anthropometric measurements (body weight, height, BMI, arm circumference, triceps and subscapular skinfold) and bioimpedance analysis (BIA) of body composition (FFM, FM, Muscle Mass, TBW).

Height and length were measured with a Seca anthropometer (Hamburg, Germany) (> 18 months) and infantometer Seca (Hamburg, Germany) (< 18 months), with accuracy 0,5 cm. Body weight was assessed using a Radwag WPT 60/500W medical scale (Radom, Poland), with accuracy 100g (> 18 months) and 10g (< 18 months). Measurements were performed according to technique described by Martin and Seller [3]. The results were adjusted to body mass and height percentile charts designated for the Polish population [4]. Underweight was diagnosed when body mass was below 10^{th} percentile and severe underweight was defined as below 3^{rd} percentile. Height and length below 3^{rd} percentile classified as short stature. Skinfold was measured with calliper with accuracy of 1 mm. The arm circumference was taken with a medical tape (accuracy of 0,1 cm). Nutritional status was estimated on the basis of BMI percentile charts published by the WHO for children and adolescents (birth-19 years of age) [5-6]. Underweight was diagnosed for BMI below the 15th percentile whereas severe underweight when it was below 3^{rd} percentile. Fat mass was calculated via the Slaughter equation, using skinfold value [7]. Muscle mass was estimated by means of Frisancho index [8]:

arm circumference without fat mass
= [arm circumference - (π x arm skinfold)]

Electric bioimpedance analysis (Maltron BIO SCAN 920-2, Rayleigh, U.K.) was used to assess fat free mas (FFM), total body water (TBW), intracellular water (ICW), extra cellular water (ECW), muscle mass (MM) and bone mass (BM). The measurement was accurate to 0,1 kg for muscle mass, fat mass and fat free mass and 1% of their percentage content. All BIA measurements were obtained using tetra polar system, i.e. four self-adhesive electrodes. The data were obtained during a pediatric examination, with patients wearing only underwear. To minimize testing errors, the patients were in a supine position for 5-10 minutes before the test, with limb loose at an angle of 30°-45° in the long axis to the torso [9].

The reference group consisted of 33 healthy children (14 girls and 19 boys) age 9 months-18 years (mean age 116 ± 65 months, median 137 months). The children in this group had no chronic or acute diseases and were hospitalized due foreign body in the digestive tract or planned corrective orthopaedic plastic surgery. The study protocol was approved by the local Bioethics Committee.

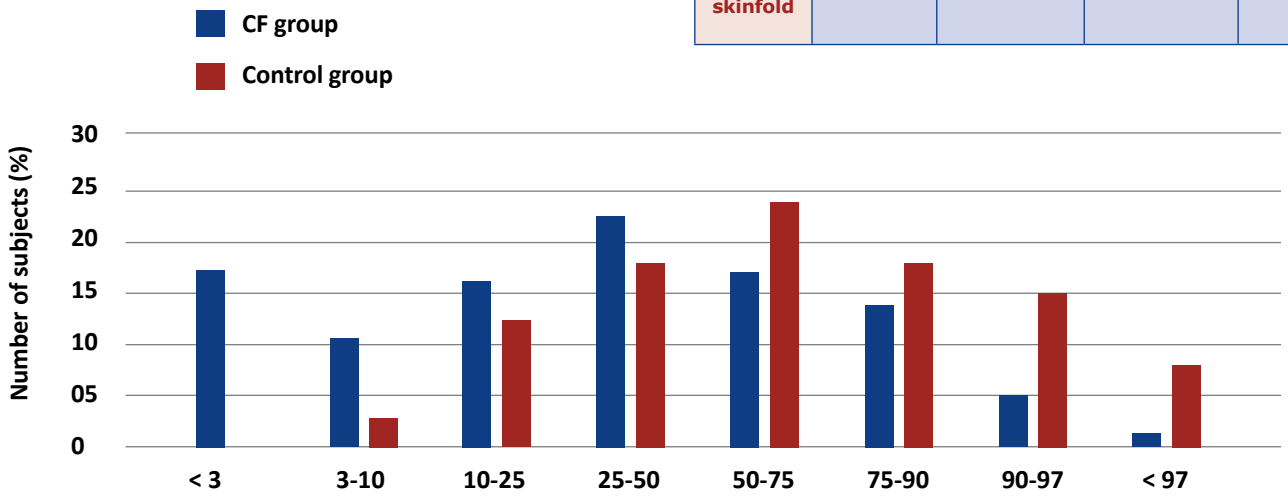
Results

There were significant differences in anthropometric measurements between children with CF and healthy ones. In accordance with the Polish percentile charts, underweight was diagnosed in 28% of the study group and severe underweight (< 3pc) affected 17.33% of these children [4] [see Graph1]. Short stature (< 3pc) was diagnosed in 18.7% of the patients [see Graph 2].

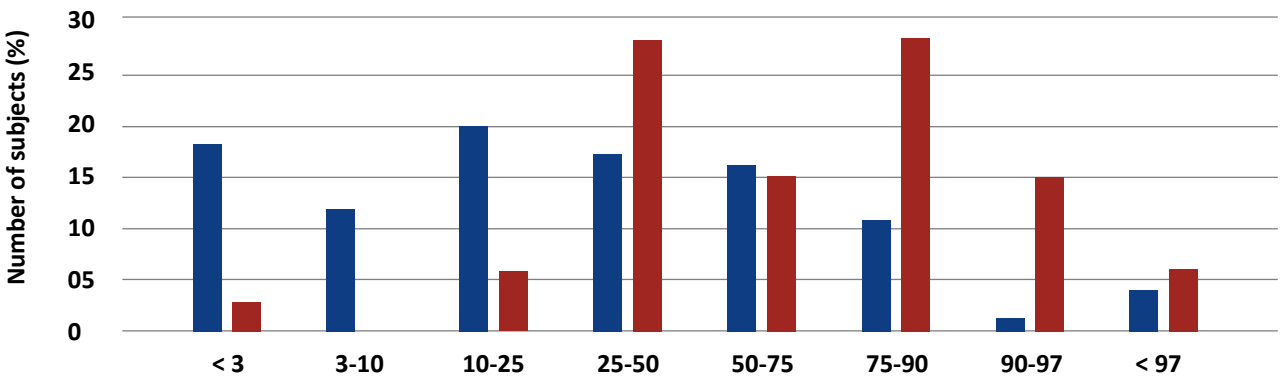
Children with CF had significantly smaller arm circumference than healthy children, for both girls and boys (p = 0.019) [Table 1]. Triceps skinfold in the CF group was in the range between 4.0 mm and 25 mm (mean 13,6 mm ± 4,5) and the mean value was significantly lower than in the reference group (p = 0.000). The sub scapular skinfold in the study group was 12.55-29 cm (mean 11.6 ± 5.2 cm) and was also smaller than in the control group [Table 1].

Table 1. Mean BMI and anthropometric features in the CF and reference groups

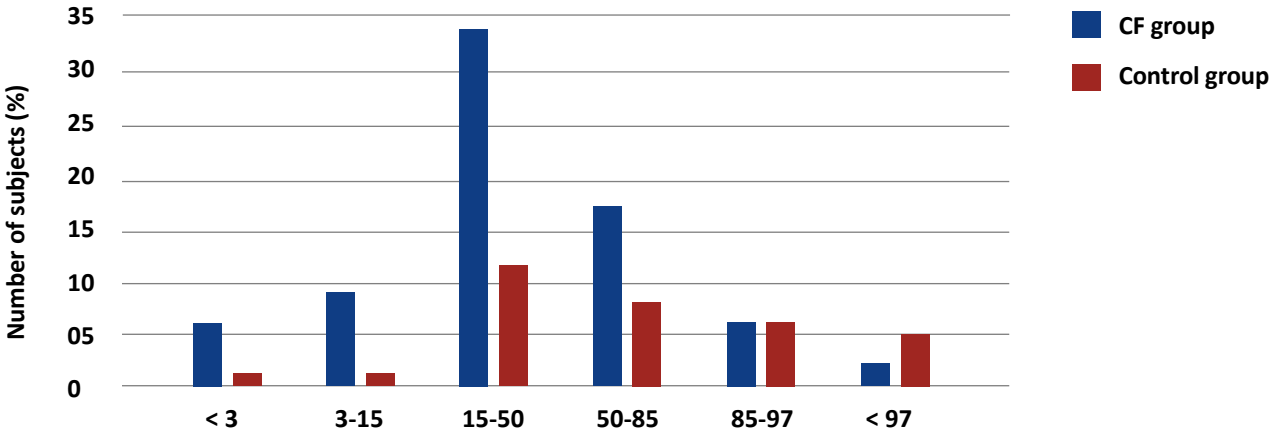
	Sex	Children with CF n = 75	Reference group n = 33	Significante of differences
Arm circum-ference [cm]	**Both**	**19,10 ± 3,30**	**22,0 ± 5,00**	**p = 0,019**
	Girls	19,16 ± 3,51	20,59 ± 5,17	p = 0,0051
	Boys	19,1 ± 3,16	22,92 ± 5,53	p = 0,000
BMI [kg/m²]	**Both**	**16,80 ± 2,2**	**19,0 ± 4,0**	**p = 0,015**
	Girls	16,76 ± 2,32	18,02 ± 3,17	p = 0,0143
	Boys	16,79 ± 2,12	19,2 ± 5,25	p = 0,0179
Triceps skinfold	**Both**	**13,6 ± 4,5**	**20 ± 7**	**p = 0,000**
Subsca-pular skinfold	**Both**	**11,6 ± 5,2**	**18 ± 8**	**p = 0,000**



Graph 1. Percentage distribution of body weight values in children with CF and the reference group. Palczewska, Niedźwiedzka (IMiDz) 1999



Graph 2. Percentage distribution of body weight values in children with CF and the reference group. Palczewska, Niedźwiedzka (IMiDz) 1999



Graph 3. Percentage distribution of body weight values in children with CF and the reference group. WHO BMI Percentile Charts

Based on the WHO standards, 20% (15) of patients with CF had BMI < 15th percentile and 8% (8 patients) were severely underweight (< 3 percentile) [Graph 3].

The results analysis showed that mean content of fat tissue in children with CF was lower than in healthy ones. Fat free mass was estimated indirectly (FFM = 100% - FM). Mean percentage of fat mass (FM%) was higher in the study group compared to the control group (p = 0.000). Fat free mass was also evaluated on the basis of arm circumference by means of Frisancho equation [8]. There was difference between the two groups (p = 0.0222). Neither the mean FFM% nor mean FM% in the study group was different from the control group. Girls with CF had higher mean fat content than boys with CF (p = 0.006). There was tendency to lower TBW in children with CF in comparison with healthy children (p = 0.008) together with lower ICW (p = 0.049) [Table 2].

Table 2. Comparison of body composition parameters obtained using electrical bioimpedance in the CF and reference groups

Body composition parameters	Children with CFn = 75 (n = 75)				Reference group (n = 33)				p
	Mean ± SD	MIN	MAX	Median	Mean ± SD	MIN	MAX	Median	
FFM [kg]	19,16 ± 3,51	5,6	60,0	23,5	32,0 ± 18,0	8,3	63,0	27,8	0,108
FFM [%]	19,1 ± 3,16	2,6	91,0	83,6	81,0 ± 8,0	65,5	96,0	81,6	0,424
FM [kg]	19,16 ± 3,51	0,9	18,0	5,2	9,0 ± 7,0	0,5	27,0	7,2	0,090
FM [%]	16,76 ± 2,32	7,1	35,0	16,3	19,0 ± 8,0	3,8	35,0	18,4	0,311
TBW [L]	16,79 ± 2,12	4,0	41,0	17,2	24,0 ± 12,0	6,8	46,0	21,0	0,080
TBW [%]	19,16 ± 3,51	46,6	87,0	61,6	62,0 ± 8,0	51,1	84,0	59,8	0,243
ECW [L]	19,1 ± 3,16	1,5	18,0	6,5	9,0 ± 4,0	2,9	18,0	7,0	0,175
ECW [%]	19,16 ± 3,51	30,5	50,0	37,6	37,0 ± 5,0	29,3	48,0	36,0	0,182
ICW [L]	16,76 ± 2,32	2,5	23,0	10,9	15,0 ± 8,0	3,9	32,0	13,9	0,049
ICW [%]	16,79 ± 2,12	49,8	70,0	62,4	63,0 ± 5,0	51,8	71,0	64,0	0,182
ECW/ICW	16,76 ± 2,32	0,4	1,0	0,6	1,0 ± 0,0	0,1	1,0	0,6	0,184
Muscle mass [kg]	16,79 ± 2,12	1,8	29,0	9,0	14,0 ± 9,0	2,5	30,0	11,9	0,133

ECW – extra cellular water, FFM – fat free mass, FM – fat mass, ICW – intra cellular water, TBW – total body water

There was a positive relationship between anthropometric and bioimpedance values of FM% (p = 0,12; R = 0,288) and FFM% (p = 0,59; R = 0,219), whereas the Frisancho index was significantly correlated to muscle mass (compatibility 82%) (p = 0,00; R 0,817).

After a year of follow-up, the mean body mass in the study group increased to 34.8 ± 13.7 kg. Underweight was diagnosed in 41.2% children and 10 children (19.2%) were severely underweight (< 3rd percentile) [Table 3]. Thus, there were more underweight children than 12 months earlier, an increase by 11% (3^{rd}-10^{th} percentile). At the same time, the number of children with body mass > 50 percentile decreased.

There was significant difference in height as well. After a year, the mean height was 140.5 ± 24.5cm and there were 3% more stunted children (height < 3^{rd} percentile) than 12 months earlier [Table 3]. However, there were more children whose height ranged between 25^{th} and 50^{th} percentile.

The mean subscapular and triceps skinfolds were thicker after a year: 15.2 ± 4.8 mm and 13.2 ± 4.2 mm respectively [Table 3]. According to the WHO standards, underweight affected 33.3% children suffering from CF, 13.7% were severely underweight. Anthropometric measurements revealed that children form study group had significantly more fat mass content (p = 0.003) and less fat free mass after a year of follow-up. Similarly, in the BIA there was also more FM (kg) and less FFM (kg). The differences in the Frisancho index revealed statistically significant reduction of muscle mass after a year (p = 0,018) [Table 3].

It was observed that children with a lower body mass percentile have worse spirometry results (FEV_1, FVC, FEF_{25-75}) [Table 4]. In addition, no relationship was observed between the remaining somatic features and lung function.

Discussion

Cystic fibrosis is one of the most prevalent autosomal recessive genetic disorders in the Caucasian

Table 3. Comparison of mean body components and somatic features in CF children obtained on the day of the initial examination and after one year

Somatic features	Children with CF – initial examination (n = 75)		Children with CF – 12 months later (n = 51)		p
	mean	SD	mean	SD	
Body mass [kg]	30,0	15,7	34,8	13,7	0,000
Body height [cm]	128,5	30,5	140,5	24,5	0,000
BMI [kg/m2]	16,8	2,2	16,8	2,2	0,722
Arm circumference [cm]	19,1	3,3	19,5	2,8	0,847
Triceps skinfold [mm]	13,6	4,5	15,2	4,8	0,006
Subscapular skinfold [mm]	11,6	5,2	13,2	4,2	0,006
Anthropometric FFM [%]	77,5	6,5	75,2	5,5	0,003
Anthropometric FM [%]	22,5	6,5	24,8	5,5	0,003
Frisancho index	14,9	2,7	14,7	2,3	0,018
BIA – FFM [kg]	25,2	12,5	29,6	13,3	0,000
BIA – FFM [%]	81,2	10,9	82,7	6,4	0,771
BIA – FM [kg]	5,8	3,8	6,7	4,9	0,399
BIA – FM [%]	17,6	6,0	17,3	6,4	0,896
BIA – TBW [L]	18,6	8,6	21,1	7,6	0,000
BIA – TBW [%]	62,2	6,7	61,8	6,2	0,201

Table 4. Comparison of lung function with somatic features and body composition parameters obtained by the method of anthropometry and electrical bioimpedance in children with CF

	FEV_1% (n = 55)		FVC% (n = 55)		FEF_{25-75}% (n = 55)	
	R	p	R	p	R	p
BMI [kg/m2]	0,120	0,383	0,199	0,144	-0,058	0,674
Body mass [percentile]	0,360	0,007	0,361	0,007	0,420	0,001
Body height [percentile]	0,252	0,064	0,250	0,066	0,408	0,002
FFM [%] anthropometry	-0,161	0,239	-0,193	0,159	-0,003	0,985
FFM [%] bioimpedance	-0,003	0,985	0,000	0,998	0,028	0,837

BMI – body mass index, FEV_1 – forced expiratory volume in 1 second, FFM - fat free mass, FEF_{25-75} – forced expiratory flow at 25-75% of vital capacity, FVC – Forced vital capacity

population [10]. The screening program performed in Poland during 2006-2010 helped to diagnose CF in 221 newborns (out of 1 212 487) and the incidence was estimated 1/4394 in Polish population [11]. Despite significant improvement in diagnosis and treatment of CF, several issues concerning both the disease and its complications need to be solved. For example, there is no gold standard for the assessment of nutritional status in children with CF, despite the fact that it is an important prognostic factor, particularly regarding the condition of the respiratory system. Walkowiak et al. emphasized the necessity of holistic evaluation of physical development [12]. On the other hand Sharma et al. proved that malnutrition was an important prognostic factor for the lifespan [13].

There are only few studies on nutrition in Polish patients with CF. Tutak-Słupska et al. found that 40% of children with CF in Bydgoszcz were undernourished (< 10^{th} percentile) and 24% of them were severely undernourished (< 3^{rd} percentile) [14]. Moreover, 28% were stunned and 16% had height < 3^{rd} percentile. A prospective study performed at the Institute of Mother and Child in Warsaw demonstrated that children suffering from CF had lower BMI, lower arm circumference, lower Frisancho index and scarce fat tissue compared to healthy children [8, 15]. The same study group was examined 4 years later and boys had less dynamic physical development (growth and body mass gain) whereas girls slower body mass gain in comparison with reference group [15]. A study from a different part of Poland revealed that stunting and even more frequent wasting are still observed despite nutritional treatment [16]. In our study we found that despite of the increase in mean values of body mass and height, the percentage of children who were underweight (from 28% to 40.6%) and severely undernourished (from 13% to 21,6%) has increased. Short stature affected 21.6% (18.6% preliminary). Our results show that anthropometric measurements (particularly body mass) worsen over time and one may conclude that so does malnourishment.

We know that body composition measurement methods and techniques should not be used interchangeably [17]. Similarly, King et al. compared 76 adults with CF in Australia using anthropometry, BIA and dual energy x-ray absorptiometry (DXA) [18]. Their results indicated a correlation between the findings obtained from various methods, but the there was a significant difference between the values. They observed false results due to CF-specific conditions (e.g. hypernatremia interfering with BIA), as well as improper patient preparation. These authors postulated that BIA should not be the reference method for assessing body composition in adults with CF. Our results also show that there are significant differences in the FM percentage and FFM measurements obtained via anthropometry and BIA and they coincided in only 29% and 22% of the patients respectively. However, when assessing the amount of muscle mass the results were strongly correlated.

There are many cross-sectional studies about the body content of children with CF, however few of them are prospective. Such, it is difficult to compare the results and make conclusions adjustable for whole population of children with CF. These studies used various

methods for body content measurement, the groups were different in terms of age and number and ethnicity.

Charatsi et al. found that patients with preserved BMI and weight may have FFM depletion and may be at risk of severe pulmonary disease [19]. Moreover, using DXA Sheikh et al. found lower FFM in patients with CF [20]. Doulgareki et al. showed that children with CF and meconium ileus have lower bone mineral density and lower fat mass in DXA compared to those with CF alone [21]. FFM was lower among children with CF and there was a positive correlation between respiratory efficiency and FFM in a study by Alvares [22]. In another study of 18 participants 12-39 years of age, FFM evaluated by BIA correlated with respiratory function better than BMI [23].

In our study, we observed that mean percentage of FM in children with CF was smaller but their muscle muss content was similar to healthy children. Data from the follow-up examination revealed a significant reduction of FFM% and mean value of Frisancho index as an indicator of % muscle mass in body. This reduction is an alarming phenomenon in children with CF because FFM reflects their clinical condition. It is well-known that muscle mass is the biggest protein and energy source during malnutrition [24]. Since the best indicator of energy expenditure in both health and illness is precisely muscle mass. In 1982 Miller et al. noticed that during chronic inflammatory disease and excessive breathing effort, catabolic processes in muscles increase [25]. Similarly, Umałowska et al. demonstrated that chronic *Pseudomonas aeruginosa* infection affects nutritional condition and correlates with reduction of both TBM and FFM [26]. In chronic lung disease progressive muscle mass loss due to the increase in resting energy expenditure on one hand, and scarce dietary protein supplementation on the other, is well known. Emphysema results in diminished effectiveness of the respiratory muscles, but malnutrition plays its part too [27].

There are many articles about the relation between FFM and diminished strength of respiratory muscles in patients with CF, which results in impaired function and worse spirometry results as well as diminished coughing reflex [28-31]. However, chronic lung disease as well as numerous infections promote catabolism and as the FFM is reduced the chronic lung disease is aggravated [32]. Meta-analysis by Calella et al. demonstrated that in patients with cystic fibrosis fat free mass and bone mineral density are lower than in healthy children, which leads to lower muscle strength [33].

The treatment of choice in CF which could influence protein metabolism and increase fat free mass is a protein-rich diet, anabolic steroids and physiotherapy [34]. Aerobic exercise increases the life expectancy of children with CF and physical activity increases muscle strength, improves quality of life [35-38] and alleviates airways clearance. Regular FFM assessment is very important because it allows fast introduction of proper therapy if FFM% starts to diminish.

Conclusions

We demonstrated that despite the significant progress in the diagnosis and treatment, underweight and short stature still affect many of patients with CF and progress with time. Deteriorating changes such as fat free mass loss take place in the course of CF. Diagnostic tests of nutritional abnormalities include anthropometry and determination of different body components via bioelectrical impedance. They should be done in early age as that enables faster implementation of nutritional treatment. These measures should be accompanied by physical activity especially in patients with FFM loss.

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RESEARCH ARTICLE

CT negative subarachnoid hemorrhage in the Emergency Department

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Abstract

Background: Subarachnoid hemorrhage (SAH) is rare but potentially life-threatening cause of acute headache. First diagnostic test performed in the Emergency Department (ED) for acute "thunderclap" headache is computed tomography of the head (CT) without contrast enhancement. Negative non-contrast head CT may be erroneously interpreted as an exclusion of SAH and lead to ED discharge. The consequences of overlooking SAH are of special interest to the Emergency Physician. The aim of this study was to assess prevalence and clinical picture of CT-negative cases of SAH admitted to the ED. **Material and methods:** Retrospective analysis of charts of patients admitted to the ED and diagnosed with SAH during 18 consecutive months. **Results:** Our data gives information about clinical picture of patients with CT-negative SAH and their further clinical course. Out of 126 patients diagnosed with SAH, 5 (4.0%) were diagnosed with SAH despite negative non-contrast head CT scan. All cases were diagnosed by means of lumbar puncture and analysis of cerebrospinal fluid. In all patients with CT-negative SAH computed tomographic angiography (CTA) was performed and no vascular abnormalities were found. In one case digital subtraction angiography was performed due to equivocal CTA picture and it demonstrated small unruptured aneurysm of the medial cerebral artery. All patients with CT-negative SAH were admitted to a neurological ward and later discharged from the hospital without neurological deficit. There were no episodes of clinical deterioration and none of the patients required an urgent neurosurgical intervention. **Conclusions:** Although lumbar puncture remains a gold standard in exclusion of SAH, head CT scan without contrast enhancement appears to be a satisfying diagnostic tool in ED.

Keywords: emergency department · Computed Tomography · cerebral aneurysm · subarachnoid hemorrhage

Citation

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Introduction

Headache is the cause of approximately 2% of Emergency Department (ED) visits [1]. The most important aim of the assessment at an ED is exclusion of a life-threatening disease. One of the potentially devastating conditions in differential diagnosis of severe headache is subarachnoid hemorrhage. Although SAH counts for only 1-3% headache-related ED visits, ruling out this potentially lethal condition is crucial for the ED physician [1]. Early diagnosis of SAH allows early aggressive treatment and help to prevent re-bleeding episodes which happen in 26-73% of SAH patients in the days-weeks after the primary bleeding incident [2]. Non-contrast head computed tomography (CT) remains gold standard in diagnosing of SAH [3]. Common diagnostic error is failure to perform a non-contrast head CT scan in patients with clinical suspicion of SAH (headache, nausea and/or vomiting, photophobia, neck stiffness, episodes of loss of consciousness, focal neurological deficits) [2]. Unfortunately, non-contrast head CT scan is not a perfect diagnostic tool because its sensitivity decreases if performed more than 6 hours after symptom onset. Furthermore, there is a group of patients with a normal head CT scan, who still have a strong clinical suspicion of SAH [4]. The next diagnostic procedure in CT-negative cases should be lumbar puncture (LP) with examination of cerebrospinal fluid [5]. Although LP is a frequently performed procedure in the ED, it may result in complications like post-lumbar puncture headache, epidural hematoma, cortical vein thrombosis and reversible cerebral vasoconstriction syndrome [6-7]. Moreover, the decision to continue diagnostic process and perform lumbar puncture significantly prolongs ED length of stay [6].

The primary aim of our study was to assess the prevalence of CT-negative SAH at a single ED. Our secondary aim was to analyze the clinical picture of patients diagnosed with CT-negative SAH and the further course of their disease. Consequences of ED discharge of patients with SAH suspicion and negative non-contrast head CT is of interest to the Emergency Physician community [8].

Material and methods

We retrospectively analyzed anonymized clinical data of patients admitted to the Emergency Department of the Medical University of Gdańsk and diagnosed with SAH in 18 consecutive months (January 2015-June 2016). We searched for information about the following diagnostic procedures: clinical examination, non-contrast head CT, cerebrospinal fluid analysis (if lumbar puncture was performed), computed tomographic angiography (if performed), cerebral arteriography (if performed). On the basis of this analysis patients diagnosed with SAH with negative non-contrast CT were identified and their clinical data were re-evaluated.

In each patient a non-contrast head CT scan was performed to rule out any potentially life-threatening condition. A radiology specialist assessed each CT scan. If the head CT scan was normal (CT-negative) but the clinical presentation was highly suspicious for spontaneous SAH, a diagnostic lumbar puncture was performed. All conscious patients gave their informed consent prior to undergoing the lumbar puncture procedure. If the patient was presenting with altered mental status and the lumbar puncture was necessary for further, potentially life-saving diagnostic procedures, the clinical context was analyzed and final decision was made by two physicians (neurologist and Emergency Medicine specialist) and documented in the patient's chart. There were 60 such cases in our sample. For better understanding the link between the clinical picture and CT/LP results in CT-negative subjects, we calculated their score according to the Ottawa SAH Rule [7]. There were no additional procedures performed as part of this research project, therefore the local Ethics Committee approval was not necessary.

Results

Our data shows clinical picture of patients with CT-negative SAH and further course of their disease. We identified the records of 126 patients with subarachnoid hemorrhage admitted to our ED during January 2015-June 2016. SAH was diagnosed by head CT without contrast enhancement in 96.0% of patients (n-121). There were 5 (4.0%) CT-negative patients who were diagnosed with SAH via CSF analysis. Clinical data of CT-negative and CT-positive patients were presented in Table 1.

Manifestation of CT-negative SAH was not specific. Although all 5 patients complained of headache, in 2 cases vomiting was present. In one case, headache was accompanied by neck stiffness as a manifestation of meningeal syndrome. The average time from first symptoms to head CT was 8 hours with 3 patients exceeding the 6-hour window. Taking into consideration well-known risk factors, one of the patients had history of well-controlled hypertension and chronic alcohol abuse. None of the patients were smokers or received anticoagulant therapy. Family history was not significant. All patients in the CT-negative group were assessed as Grade 1 in the Hunt & Hess classification while the average grade in the CT-positive group was 2,5. All patients with

Table 1. Clinical data of the CT-positive and CT-negative patients

	CT-positive group	CT-negative group	p
Age (years, mean	55.9	50.4	NS
Sex (% of men)	43 (35.5%)	2 (40%)	NS
Headache (n,%)	98 (81%)	5 (100%)	NS
Vomitting (n,%)	53 (43.8%)	2 (40%)	NS
Meningeal symptoms (n,%)	56 (46.2%)	1(20%)	NS
Neurological deficit (n,%)	78 (64.5%)	0 (0%)	0,007
Cerebral aneurism found (n,%)	103 (85.1%)	1 (20%)	0.0032
Neurosurgical intervention (n,%)	92 (76.0%)	0(0)%	0,0011
Deaths (n,%)	34 (28.1%)	0 (0)%	NS

results of cerebrospinal fluid (CSF) analysis typical for SAH underwent CTA with no significant findings. 4 out of 5 CT-negative patients underwent cerebral angiography and an unruptured aneurysm of the middle cerebral artery was found in one subject. The score of CT-negative LP-positive subjects according to the Ottawa SAH Rule was suggesting suspicion of SAH, as shown in Table 2.

Clinical outcome in the CT-negative SAH patients group was favorable. All patients with CT-negative SAH survived and were discharged from the hospital without neurological deficit. None of those patients required any urgent surgical intervention and no episodes of clinical deterioration were observed during their hospital stay.

Discussion

Our study revealed that 4.0% of patients diagnosed with SAH at ED had a normal non-contrast head CT. This result is slightly lower than previously published findings showing percentage of CT-negative SAH between 4-20% [9-11]. The discrepancies may be partially explained with differences in parameters of CT scanner and in experience of radiologists describing the images. Nevertheless, our results demonstrated higher percentages that suggested in the meta-analysis by Dubosh et al, showing that relying solely on non-contrast head CT may lead to missing only 0.15% of SAH cases. To note, the above results were obtained for patients with "thunderclap" headache and no neurologic deficit, in whom CT was performed within 6 hours of the headache onset [12]. Williams and Sepaul while commenting these results suggested that the Emergency Physican needs to be aware that the CT scan might be negative after the 6-hour window [13].

Table 2. The score of CT-negative LP-positive subjects according to the Ottawa SAH Rule

Patient	Age ≥40?	Neck pain or neck stiffness?	Witnessed loss of conscious-ness	Onset during exertion?	"Thunder-clap" head-ache?	Limited neck flexion?	Total score	Suggestive for SAH?
Patient 1	0	0	1	0	0	0	1	YES
Patient 2	1	1	0	0	1	0	3	YES
Patient 3	1	0	0	0	1	0	2	YES
Patient 4	1	0	0	0	1	0	2	YES
Patient 5	**1**	**1**	**0**	**0**	**1**	**1**	**4**	**YES**

Legend: Answer YES was scored 1; answer 2 was scored 0

On the contrary, our observations suggest that such practice may lead to overlooking a significant percentage of SAH cases, particularly because all of the CT-negative patients in our sample presented with a "thunderclap" headache and no neurologic deficit.

All 5 of our patients with CT-negative SAH presented with thunderclap headache and only one of them had neck stiffness. This very unspecific clinical presentation is a known feature of SAH. Carpenter et al. confirmed that in their meta-analysis that there are no clinical findings allowing to rule in or to rule out SAH in patients with acute headache without further diagnostic workup [14]. Our results emphasized that patients with thunderclap headache require thorough diagnostics even with negative head CT. Moreover, it should be noted that there was one case of unruptured aneurysm revealed in patients with negative head CT that suggests that detailed vascular imaging may lead to significant findings. This finding stays in line with results of Chong et al., who discovered presence of vascular abnormalities in over 40% of subjects with CT-negative SAH [15].

All patients with CT-negative SAH from our group had a good prognosis – there were no deaths in that group as well as no clinical deterioration (e.g. re-bleeding), or need for urgent neurosurgical intervention. This is in concordance with finding of Mark et al, who analyzed a population of probably overlooked SAH. The authors analyzed clinical course of patients finally diagnosed with SAH who through 14 days prior the diagnosis were examined due to suspicion of SAH with negative conclusion. They found that probable overlooking of SAH did not influence negatively their prognosis [16]. Chong et al. reported similar observation as only 1.3% of patients with CT-negative SAH experienced further re-bleeding [15].

Although subarachnoid hemorrhage is a relatively rare cause of headache, failure to recognize it is a familiar clinical scenario for ED physicians [17]. Most of the patients with symptoms suggestive of intracranial hemorrhage are diagnosed in ED, which are known worldwide to be overcrowded [18]. The more laboratory tests, diagnostic images and procedures are performed, the more prolonged length of ED stay and the more patients undergoing assessment and treatment at the same time [19]. Excessive number of patients being treated in ED simultaneously may cause increased hospital mortality [20]. Anecdotally, the most primary purpose of the ED physician is to identify patients in life-threatening condition and to initiate prompt and adequate treatment.

Initial misdiagnosis of SAH may lead to discharge from the ED, followed by a potentially catastrophic re-bleeding episode [2, 21]. Optimizing the quality of diagnostics and care of patients with suspected SAH is an important issue in recent Emergency Nedicine and Neurology literature. One of the solutions for prolonged diagnostics of headache in ED is extending imaging after originally negative non-contrast head CT scan to include CT-angiography if SAH remains part of the differential diagnosis, which may significantly reduce the risk of overlooking aneurysmal SAH [11]. Another approach is to focus on assessment of initially performed non-contrast head CT scan, as radiological evidence of SAH is frequently unrecognized [7].

As clinical rules are spreading across the Emergency Medicine community, there is also recently validated Ottawa SAH Rule that can help a physician to rule out subarachnoid hemorrhage in a certain group of patients [22]. Identifying the population with extremely low risk of a life-threatening cause of headache can also help a clinician to use popular worldwide shared decision-making model in which both a patient and medial practitioner understand and accept the risk involved in the decision to finish the diagnostic process [23-24]. Nevertheless, lumbar puncture remains the most sensitive tool to exclude SAH in all cases where the clinical presentation is highly suspicious, clinical rules not applicable and radiology inconclusive for SAH [14, 25].

Conclusions

Subarachnoid hemorrhage continues to be one of the most important parts of differential diagnosis in population of patients visiting the ED due to headache, head CT scan without contrast enhancement appears to be a satisfactory diagnostic tool to exclude this potentially lethal condition. In our study, only 4.0% of subarachnoid hemorrhages were diagnosed despite negative non-contrast head CT. The clinical course of CT-negative SAH was mild. It can be presumed that lumbar puncture may be a decisive diagnostic procedure for a minor group of patients with high clinical risk of SAH and inconclusive preceding diagnostic process. This data may increase awareness of incidence of CT-negative SAH and help physicians to properly plan diagnostic procedures after negative head tomography.

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RESEARCH ARTICLE

Sciatica: Internet Search Trends

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Abstract

Background: Sciatica is a significant global health burden with a lifetime incidence estimated between 13% and 40%. In our study, we assessed the online health interest in sciatica and lower back pain. **Material and methods:** Google Trends, Wikipedia statistics and PubMed data were used to gauge the online public interest in sciatica and lower back pain. **Results:** In the years 2015-2019 the Wikipedia page about sciatica has ranked high in all four categories it was included in, thus demonstrating that sciatica is a significant concern for the public. Wikipedia pages about sciatica and low back pain had a respectively 28% and 90% increase in views from July 2015 to March 2019. In the last eleven years (2008-2019) Google Trends demonstrates that sciatica has had a 2-fold increase in search frequency worldwide on the web, a 6-fold increase on YouTube and a 3-fold increase on Google images. In contrast, scientific interest in sciatica is low (only 140 PubMed publications in 2018). **Conclusions:** People have a relatively high and increasing online interest concerning sciatica and back pain. As a response, we suggest that hospital staff clearly provide reliable and understandable information to their patients concerning sciatica and lower back pain treatment.

Keywords: lower back pain · sciatica · Google Trends · Wikipedia

Citation

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Introduction

Majority of patients use online resources such as Wikipedia and a Google search to learn more about their illnesses. Wikipedia, a free online encyclopedia, is one of the leading sources of healthcare information [1-2]. Google is the world's most popular search engine which produces a significant portion of online searches for information about diseases. Both these platforms collect and publish statistics on user search traffic and this information may be used for analysis. Additionally, PubMed is an online database that

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indexes all major biomedical journals and it may be used to estimate the scientific output on a particular topic. So far, studies have been conducted using these platforms to assess the overall trends of several neurological diseases including epilepsy and multiple sclerosis [3-5].

However, these online tools have not yet been used to assess the online search trends for sciatica. Hippocrates first published about "sciatic pain" more than two thousand years ago, whereas in the early 20th century Harvey Cushing helped to establish surgical treatments for this condition. Today, sciatica is a significant global health burden with a lifetime incidence estimated between 13% and 40% [6]. Given its high incidence, our aim was to assess the popularity of sciatica online using Google Trends, Wikipedia and PubMed publication data [7-8].

Methods and materials

The Wikipedia Massviews tool was used to assess the objective popularity of sciatica in the following 4 categories it was indexed under: symptoms and signs: musculoskeletal system, orthopedic problems, pain, and peripheral nervous system disorders. Sciatica was searched (as a medical condition) on Google Trends for the last full eleven years (2008-2019). PubMed results were used to estimate the number of scientific articles on sciatica for the year 2018 the following keywords were searched: "sciatica," "low back pain" and "leg pain AND lumbar AND 2018."

Results

Wikipedia findings

Over the last full five years, (2015-2019) the Wikipedia article on sciatica has ranked high in all of the 4 categories it was included in: it ranked first under *Symptoms and signs: musculoskeletal system*, first under *Orthopedic problems*, first under *Pain* and second under *Peripheral nervous system disorders*. Considering that Wikipedia is the number one source for health information for patients and health care professionals, this demonstrates that sciatica is a significant concern for the public [1]. Sciatica not only seems to be more of a concern compared to other neurological disorders, like trigeminal neuralgia or neuropathic pain, but it is the most commonly searched topic in the vast category of "pain." Furthermore, Wikipedia page views on *sciatica* and *low back pain* show a 28% and 90% increase respectively from July 2015 to March 2019.

Google findings

In the last full eleven years (2008-2019) Google Trends shows that sciatica (as a medical condition) had a 2-fold increase in search frequency worldwide on the web, a 6-fold increase on YouTube and a 3-fold increase on Google images. Lower back pain (as a disorder) exhibited a similar trend with a 2-fold increase in search frequency worldwide on the web, 8-fold increase on YouTube (see Figure 1) and a 3-fold increase on Google images from the same time period.

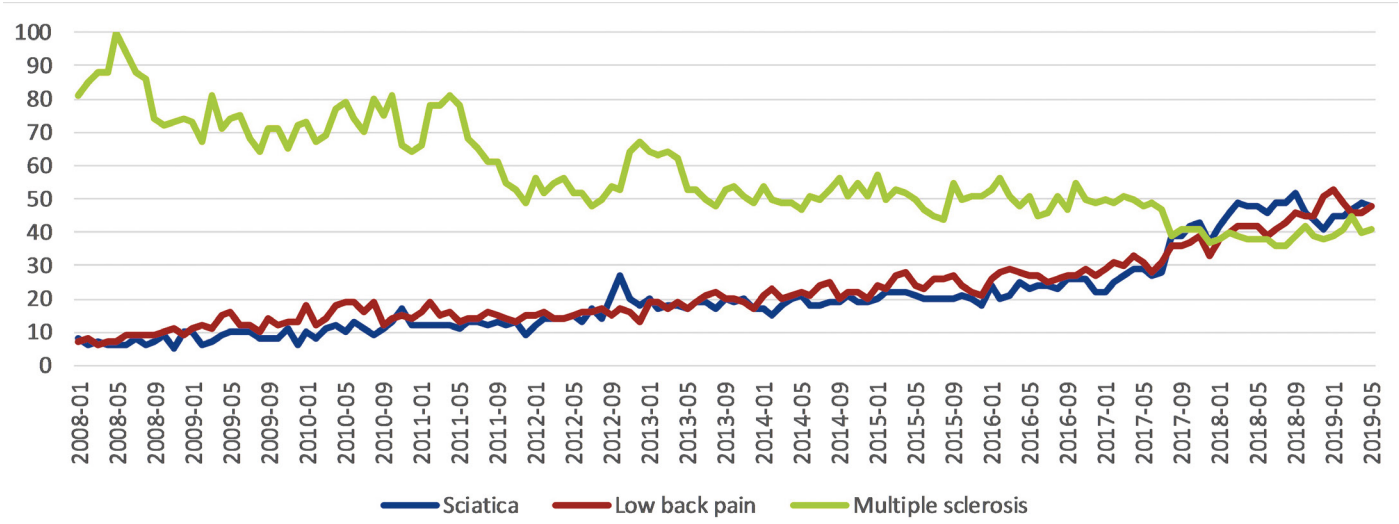

Figure 1. YouTube searches for sciatica, low back pain and multiple sclerosis from 2008 to 2019

PubMed findings

2018 PubMed statistics show that scientific interest in sciatica is low. Search query *sciatica* returned 140 articles. The combined search terms *leg pain, lumbar* and *2018* return 406 results. The results are slightly higher for low back pain (2,218 publications). This might suggest that scientists are more concerned of the problem of low back pain than sciatica, however, the varying definitions of sciatica in literature do not allow a reliable comparison of the real burden of sciatica and low back pain [9]. Nevertheless, both conditions garner a lower scientific interest when compared to another neurological condition such as multiple sclerosis (4,817 articles) as seen on Figure 1. Multiple sclerosis faced a 29% decrease of in-web searches, a 54% decrease on YouTube and a 20% decrease on Google Images between 2008 and 2019. Notably, multiple sclerosis has a far lower prevalence than sciatica or back pain.

Discussion

We found that there is an overwhelming increase in public interest on sciatica and low back pain. This finding is novel as we could not find any published study describing this trend. Perhaps this is due to the fact that online tools such as Massviews have only recently been available to highlight these trends.

Although effective medical, surgical and alternative treatment methods are available for sciatica, it is important for physicians to be aware of this pervasive condition as there is still a lack of evidence concerning the optimal treatment of lumbar disc-induced sciatica [10]. From an economic standpoint, presenteeism due to sciatica may deteriorate productivity in the workplace and undermine a country's economy [11].

There is miscommunication between patients and surgeons in regards to sciatica treatment [12]. One study found that patients felt that they were not given enough information by their surgeon regarding lumbar decompressive surgery to treat sciatica. However, the surgeons considered that they had expressed sufficient information. Due to the perceived knowledge gap, patients sought medical information from family, friends and the internet [12]. Notably, the topic “disc herniation” (a common cause of sciatica) yields low quality videos on YouTube [13-14]. Moreover, several studies show that the online information about neurological and neurosurgical diseases is too difficult for patients to understand [15-17]. Various treatments for sciatica have been recommended including bed rest, physical therapy, spinal manipulation and lumbar discectomy [18-20]. Given the broad spectrum of treatment options and the current online interest in sciatica, it would be beneficial if the scientific community provided reliable and reader-friendly information for the public.

Limitations of the analysis

Google accounted for 92% of the search engine market share worldwide from 2009 to 2018. Thus about 8% of the searches conducted on other search engines (i.e. DuckDuckGo, Bing, Yahoo!, Baidu, Yandex RU and Sogu) were not analyzed with Google Trends [21].

The definition of sciatica may differ among information-seekers. Even among physicians the exact definition of sciatica differs. Some researchers define sciatica as leg pain that extends from the back yet others restrict it to pain from specifically the lumbar nerve root [9].

The exact location and demographics of the increased online interest in sciatica could not be determined as it was not available from the platforms analyzed. Future studies may assess the age, gender, location or education level of information-seekers to pinpoint in exactly which populations saw an increase in sciatica.

Conclusion

Our study highlights that modern online tools may offer concerning public health information-seeking behavior in neurology and neurosurgery. Objective online metrics used in our paper have revealed that sciatica and back pain garner relatively high online interest. We suggest that hospital staff clearly highlight the causes, pathophysiology, diagnosis and management of sciatica in an easy to understand way via in-hospital leaflets, online materials and public relations work. We encourage physicians to be mindful of the high public interest in sciatica to mediate patient expectations regarding their prognosis and sciatica treatment options.

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REVIEW ARTICLE

How to deal with patients with atrial fibrillation during an epidemic?

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Abstract

Patients with atrial fibrillation (AF) due to old age and comorbidities are at a higher risk of SARS-CoV-2 infection. These patients should protect themselves by limiting contact with other people to an absolute minimum and they should be educated about hygiene, including careful hand washing. In general, the principles of antiarrhythmic drug treatment of quarantined, infected and asymptomatic individuals remain unchanged. In the hospital setting it is important to remember about possible interactions between anticoagulants, antibiotics, antiarrhythmic, antiviral and antimalarial drugs. The current pandemic also led to limitations regarding the implantation and control of implantable devices to an absolute minimum.

Keywords: atrial fibrillation · coronavirus · infection · SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2 · COVID-19 · Coronavirus disease 2019 · non-vitamin K oral anticoagulants (NOACs)

Citation

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Introduction

In March of this year the World Health Organization (WHO) announced that the current global coronavirus-related situation (coronavirus disease 2019, COVID-19) is a pandemic. The causative agent the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the highly pathogenic β-coronavirus family. Besides pneumonia, SARS-CoV-2 may cause severe respiratory disorders [1-2]. This virus spreads via droplets and through direct contact with an infected person. The cases of spreading the virus by air have not been confirmed and although it is not considered significant, it cannot be ignored when medical procedures involving the formation of aerosol are carried out [3]. The conjunctiva of the eye

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is also very likely to be infected due to fluid contamination. The virus incubation period is on average 4-5 days. According to data published by the WHO, the time to onset of symptoms is usually 5 days and no later than 11.5 days [4].

A positive epidemiological history is an important step in the diagnosis of SARS-CoV-2 infection. The epidemiological factors in the period of 2 weeks preceding the onset of the disease are: a visit to an area where the disease occurs, contact with a COVID-19-positive person or contact with a symptomatic person (e.g. fever and respiratory symptoms) from the area where the infection occurs.

Clinically the infection presents primarily with fever and/or respiratory symptoms. Radiological signs in computer tomography of the lungs are frequent. Whereas laboratory tests may reveal normal or decreased white blood cell count or decreased lymphocyte count [5].

Material and methods

This is a narrative-type review of current English-language literature on the subject of COVID-19 and atrial fibrillation. No statistical analysis was performed.

Results

What is known so far about COVID-19 and cardiovascular diseases?

Infection of SARS-CoV-2 is caused by binding of the viral spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor. The binding is followed by an activation of the viral spike protein by transmembrane protease serine 2 (TMPRSS2) [6].

ACE2 receptor is expressed in the lung and is the predominant way of entry. ACE2 is expressed also in the heart. ACE2 receptor as well is expressed in the intestinal epithelium, vascular endothelium, and the kidneys. This explains the multi-organ dysfunction occurrence in SARS-CoV-2 infection [7]. Unfortunately, there is increasing evidence showing that COVID-19 is connected with increased morbidity and mortality in patients with cardiovascular diseases.

The case fatality rate (CFR, number of deaths/number of those diagnosed) is a very important parameter. In patients with no comorbidities the CFR is 0.9%, whereas in patients with cardiovascular disease (CVD) it is increased to 10.5%. For patients with diabetes mellitus (DM) the CFR is 7.3%, while 6.3% for chronic obstructive pulmonary disease, 6% for hypertension (HTN) and 5.6% for cancer [8].

Recent meta-analysis of eight studies from China including 46,248 infected patients showed the most prevalent commodities were HTN (17 ± 7%, 95% CI 14-22%) and DM (8 ± 6%, 95% CI 6-11%), followed by cardiovascular diseases (5 ± 4%, 95% CI 4-7%) [9]. Myocardial injury in COVID-19 was proved by elevated cardiac biomarkers. In the Chinese study of 138 hospitalized patients with COVID-19 in Wuhan elevated high sensitivity troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities were present in 7.2% of patients overall, and 22% that required treatment at an intensive care unit [10].

The report from the National Health Commission (NHC) of China comments that there is a subset of COVID-19 patients who presented with palpitations and chest pain, not the typical fever and cough [11]. Based on limited data, it seems that the incidence of fulminant myocarditis and cardiogenic shock is low [12].

Problems with INR assessment

In March 2020 a substantial number of laboratories in Poland were either closed or had limited working hours. This way the access to INR assessment became limited. In such circumstances it is advisable to switch from vitamin K antagonists to NOACs whenever it is possible, except for patients with artificial heart valves, recent implantation of biological valves, rheumatic stenosis or anti-phospholipid syndrome.

It is noteworthy that patients on NOAC cannot be deprived of the assessment of kidney function parameters. The test of choice is Creatinine Clearance (CrCl) calculated using the Cockroft-Gault equation. Patients taking NOACs need to have a renal function test at least annually in order to modify the dose if needed. If the patient's renal function is impaired (i.e. CrCl ≤ 60mL/min), a more frequent evaluation is recommended. The minimum frequency of renal function testing (in months) can be obtained by simply dividing the patient's recent CrCl by 10. In patients with additional risk factors (e.g. older age, frail, multiple comorbidities etc.), renal function may be evaluated even more frequently [13].

Is there any interaction between COVID-19 virus and NOAC?

If the patient with AF on NOAC is experiencing symptoms of COVID-19 or is suspect that may be infected with COVID-19, it is advised to consult with healthcare provider and closely follow the treatment recommendations that are given.

Depending on individual symptoms and medical history, if a patient with AF treated with NOAC is infected with COVID-19, the healthcare provider should advise if and exactly how the treatment needs to be adjusted. Until then, the patient should continue the treatment with NOAC as previously advised by the healthcare provider.

Is there any interaction between NOACs and antimalarials or antivirals?

No detailed information is available yet for many potential interactions with NOACs and drugs that are used in AF patients. NOAC producers have not conducted dedicated drug-drug interaction studies to evaluate the co-administration of NOACs and the drugs listed above. For example, the recommendation listed in the manufacturer's label for dabigatran is based on the only drug-drug interaction study conducted with ritonavir, regarding its use in the treatment of human immunodeficiency virus (HIV) [13]. Concomitant use with protease inhibitors such as ritonavir (and its combination with other protease inhibitors for example lopinavir) is not recommended. These drugs affect P glycoprotein (P-gp). As specified on the label, the pro-drug dabigatran etexilate but not dabigatran is a substrate of the transporter P glycoprotein (P-gp) [14].

P-gp inhibitors may increase exposure to dabigatran and therefore may increase the risk of bleeding. Close clinical monitoring for signs of bleeding or anemia and dose reductions may be required. P-gp inducers are expected to reduce dabigatran systemic exposure. Co-administration of potent P-gp inducers with dabigatran should be avoided.

Neither dabigatran etexilate nor its active metabolite dabigatran are metabolized by the cytochrome P450 system or have an effect on *in vitro* cytochrome P450 enzymes. Dabigatran is not expected to have any cytochrome P450 related drug-drug interactions.

No dedicated studies with antiretroviral medications such as Darunavir + cobicistat used in HIV infection and NOACs have been conducted as dedicated drug-drug interaction studies. Darunavir and cobicistat are both P-gp inhibitors. Coadministration of darunavir and cobicistat with dabigatran may result in increased dabigatran exposure and increased risk of bleeding [15].

According to dabigatran label, concomitant treatment with strong P-gp inhibitors is contraindicated. If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia), dose reductions may be required [14].

No relevant literature citations were identified in MEDLINE and EMBASE with the search terms "dabigatran" and the antimalarial or antiviral drugs such as: "chloroquine phosphate," "hydroxychloroquine" and "oseltamivir." Furthermore, no results were found for "dabigatran" and "remdesivir," "camostat," "favilavir" or "favipiravir." As always, clinical judgment should be crucial in managing every individual patient. Apixaban, rivaroxaban and dabigatran should not be used with atazanavir and lopinavir/ritonavir (see Table 1).

Table 1. Interactions of anti-coagulant, anti-platelet and fibrinolytic drugs with antimalarial and antiviral drugs used in experimental treatment of COVID-19

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	RBV	TCZ	IFN–β
Acenocoumarol	↔	↓	↔	↔	↔	↔	↔	↓	↔
Apixaban	↑	↑	↔	↔	↑	↑	↔	↓	↔
Aspirin (anti-platelet)	↔	↔	↔	↔	↔	↔	↔	↔	↔
Betrixaban	↑♥	↑♥	↔	↔	↑	↑	↔	↔	↔
Clopidogrel	↓	↓	↔	↔	↔	↔	↔	↓	↔
Dabigatran	↑	↔ or ↓	↔	↔	↑	↑	↔	↔	↔

Dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Dipyridamole	↑	↓	↔	↔	↔	↔	↔	↔	↔
Edoxaban	↑	↑	↔	↔	↑	↑	↔	↔	↔
Enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔
Heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenprocoumon	↑	↑↓	↔	↔	↔	↔	↔	↓	↔
Prasugel	↔	↔	↔	↔	↔	↔	↔	↓	↔
Rivaroxaban	↑	↑	↔	↔	↑	↑	↔	↓	↔
Streptokinase	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ticagrelor	↑	↑	↔	↔	↔	↔	↔	↓	↔
Warfarin	↑	↓	↔	↔	↔	↔	↓	↓	↔

Abbreviations: ATV – Atazanavir; LPV/r – Lopinavir/ritonavir; RDV – Remdesivir; FAVI – Favipiravir; CLQ – Chloroquine; HCLQ – Chydroxycloroquine; RBV – Ribavirin; TCZ – Tocilizumab; IFN-β – Interferon beta

Color legend

- **These drugs should not be coadministered**
- **Potential interaction which may require a dose adjustment or close monitoring**
- **Potenttial interaction likely to be weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required**
- **No clinically significant interaction expected**

Text legend

- ↑ **Potential increased exposure of the comedication**
- ↓ **Potential decreased exposure of the comedication**
- ↔ **No significant effect**
- ♥ **One or both drugs may cause QT and/or PR prolongation. ECG monitoring is advised if coadministered**

Detailed recommendations for about drug interactions with experimental COVID-19 therapies are updated regularly at: http://www.covid19-druginteractions.org/

Is there any interaction between NOACs and tocilizumab (IL6-receptor blocker)?

The manufacturers of NOACs have not conducted dedicated drug-drug interaction studies to evaluate the coadministration of NOACs and tocilizumab. According to European Medicines Agency's summary of product characteristics, tocilizumab interacts with cytochrome 450, no information on drug-drug interaction related to P-gp transport is available [16]. According to dabigatran label, dabigatran is not expected to have any cytochrome P450 related drug-drug interactions [17].

Are there any interactions between experimental COVID-19 therapies and azithromycin?

Prolonged cardiac repolarization and QT interval, imparting a risk of lethal ventricular arrhythmias including torsades de pointes, were observed in treatment

with macrolide antibiotics including azithromycin. Therefore, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as:

- current treatment with other known QT interval-prolonging drugs such as class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol) antiarrhythmics,
- electrolyte abnormalities, particularly hypokalaemia and hypomagnesaemia,
- clinically-relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin [18].

Are there any interactions between experimental COVID-19 therapies and antiarrhythmics?

See Table 2.

Table 2. Interactions of antiarrhythmic drugs with antimalarial and antiviral drugs used in experimental treatment of COVID-19

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	RBV	TCZ	IFN–β
Amiodarone	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↓	↔
Bepridil	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↔	↔
Disopyramide	↑♥	↑♥	↔	↔	↔ ♥	↔♥	↔	↔	↔
Dofetilide	↑♥	↑♥	↔	↔	↔ ♥	↔♥	↔	↔	↔
Flecainide	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↔	↔
Lidocaine (Lignocaine)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Mexiletine	↔	↑	↔	↔	↑♥	↑♥	↔	↔	↔
Propafenone	↑	↑	↔	↔	↔ ♥	↔♥	↔	↔	↔
Quinidine	↑	↑	↔	↔	↔ ♥	↔♥	↔	↓	↔

Abbreviations: ATV – Atazanavir; LPV/r – Lopinavir/ritonavir; RDV – Remdesivir; FAVI – Favipiravir; CLQ – Chloroquine; HCLQ – Chydroxycloroquine; RBV – Ribavirin; TCZ – Tocilizumab; IFN-β – Interferon beta

Color legend

- **These drugs should not be coadministered**
- **Potential interaction which may require a dose adjustment or close monitoring**
- **Potenttial interaction likely to be weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required**
- **No clinically significant interaction expected**

Text legend

- ↑ **Potential increased exposure of the comedication**
- ↓ **Potential decreased exposure of the comedication**
- ↔ **No significant effect**
- ♥ **One or both drugs may cause QT and/ or PR prolongation. ECG monitoring is advised if coadministered**

Detailed recommendations for about drug interactions with experimental COVID-19 therapies are updated regularly at: http://www.covid19-druginteractions.org/

Indications for electrotherapy and electrophysiology procedures during the pandemic

For patients from the general population (people without confirmed infection and with a negative history of risk factors for infection), it seems reasonable to postpone elective procedures such as:

- elective ablation of atrial fibrillation,
- implantation of cardiac pacemaker in case of tachycardia-bradycardia syndrome (atrial fibrillation as tachycardia) with scant symptoms.

The purpose of this restriction is to protect patients from contact with healthcare professionals and healthcare facilities, where the risk of infection is higher. Replacement of pacing systems due to a depleted battery or damaged electrodes should be carried out according to previously used procedures.

If possible, for people with suspected COVID-19 infection (people in quarantine awaiting their COVID-19 test result and with a history indicating the possibility of infection), the procedures should be postponed in all cases until confirmation or exclusion of infection.

Whereas for patients with a confirmed diagnosis of COVID-19 procedures should be carried out only if the patient has a life-threatening condition and performed in infectious disease hospitals with an electrotherapy laboratory. Otherwise, if the patient is not in a life-threatening condition, then the procedure should be postponed until the patient is cured of the COVID-19 infection or until the pandemic is over.

Postoperative pacemaker control, radiological and echocardiographic control, if possible, should be postponed until the patient's epidemiological status is confirmed. If this is not possible, the procedures should be carried out in accordance with the center's internal procedures adopted for the care of patients with COVID-19 [19].

Prior to a planned device control visit, it is recommended to make telephone contact with the patient or caregiver and to history regarding clinical events (fainting, loss of consciousness) and disturbing symptoms associated with the device placement (e.g. redness, swelling, soreness, thinning of the skin) which may indicate a local infection or perforation. When in doubt, it is recommended that the patient sends photographs of suspicious changes for verification by the supervising cardiologist.

When using telemedicine systems for implantable devices that do not use daily automatic transmissions, the date and time of the planned data transmission from the implanted device should be set.

In each case, the date of the control visit and patient transportation should be agreed upon with the supervising cardiologist (or with other staff at the clinic). The patient should not use public transportation to and from the control visit. The patient should be advised to arrive on time and if possible use personal protective equipment (mask, gloves). The clinic staff should organize the process of registration and admission of the patient in way that minimizes the number of people in direct contact with the patient [20].

Conclusions

Patients with atrial fibrillation (AF) due to old age and comorbidities are at a higher risk of severe COVID-1 cours infection. These patients should protect themselves by limiting contact with other people to an absolute minimum and they should be educated about hygiene, including careful hand washing. In general, the principles of antiarrhythmic drug treatment of quarantined, infected and asymptomatic individuals remain unchanged. In the hospital setting it is important to remember about possible interactions between anticoagulants, antibiotics, antiarrhythmic, antiviral and antimalarial drugs. The current pandemic also led to limitations regarding the implantation and control of implantable devices to an absolute minimum.

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REVIEW ARTICLE

The role of interdisciplinary cooperation in the prevention of Medication-Related Osteonecrosis of the Jaw (MRONJ)

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Abstract

Medication-Related Osteonecrosis of the Jaw (MRONJ) is considered one of the most severe complications of treatment with antiresorptive drugs. The number of patients with MRONJ has significantly increased due to the broadening of the indication to treat with bisphosphonates and other antiresorptive drugs (e.g. denosumab). Because MRONJ has a significant impact on the patients' quality of life, it is necessary to reduce the risk of such complications by implementing preventive measures, e.g. full dental and oral cavity examination for all patients qualified for treatment with angiogenesis inhibitors or antiresorptive drugs.

Keywords: bisphosphonates · denosumab · osteonecrosis

Citation

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Introduction

Bisphosphonate-Related Osteonecrosis of the Jaw was described for the first time in 2003 in a case series of 36 patients treated with zoledronic or pamidronic acid [1]. The authors described painful exposure of the maxilla and mandible that did not react to surgical nor pharmacological treatment [1]. Numerous case reports of this condition were published since and its nomenclature has been changing [2-4]. Due to the increasing number of described cases of antiresorptive drug-related osteonecrosis of the jaw bones, in 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested the term Medication

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Related Osteonecrosis of the Jaw (MRONJ) [4]. According to the current literature, osteonecrosis is a complication of treatment with bisphosphonates, denosumab and angiogenesis inhibitors [4-7].

Diagnostic criteria of MRONJ

The AAOMS position paper from 2014 indicate that MRONJ can be suspected if all of the following criteria are met:

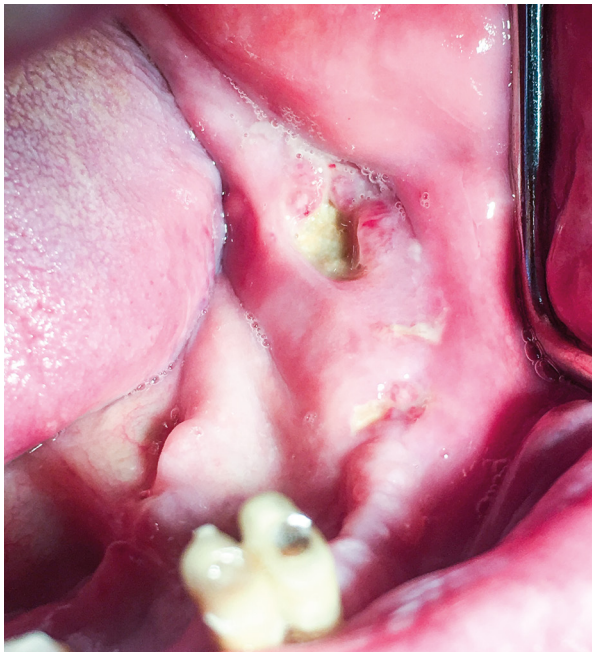
- ongoing or past treatment with angiogenesis inhibitors or antiresorptive drugs,
- exposed facial/jaw bone or an extraoral fistula in the maxilla-facial area lasting > 8 weeks,
- no previous history of head and neck radiotherapy,
- lack of metastases to the jaw bones [4].

Clinically, a patient with MRONJ may present with exposed jaw bone with a focus of necrosis, pathological fracture of jaw bone, pain, inflammation, tooth movement, extraoral fistula, oral antral or oral nasal communication [4, 8-9] [see Figures 1-3].

Because MRONJ is a relatively new diagnosis, the literature about its treatment is scant and often limited to case reports. Several national and international dental and maxillo-facial surgery associations published MRONJ treatment guidelines [4-7]. However, these guidelines are often divergent due to a limited number of treated patients and different institutional experience [10]. The treatment strategy suggested by the AAOMS seems to be useful as it is based on the assessment of MRONJ severity which then guides the decision about appropriate treatment [4, 6] [see Table 1]. Infection control, analgesia and stopping the progression of osteonecrosis are key elements of MRONJ treatment [6].

Antiresorptive drugs

Bisphosphonates are group of drugs indicated for osteoporosis, osteopenia, Paget's disease of the bone, osteogenesis imperfecta, prevention of hypercalcemia and metastasis to the bones [1, 3-4, 8, 11]. By binding to the bone matrix, bisphosphonates exert their antiresorptive activity at several stages, e.g. inhibition of osteoclast precursors' maturation, inhibition of matu-



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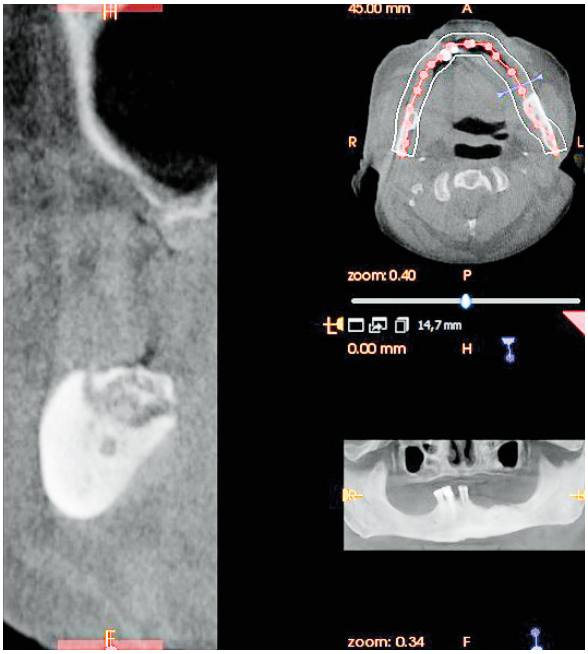

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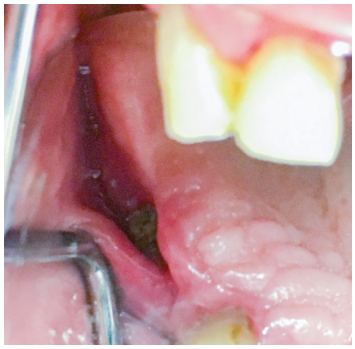
Figure 1. Example of Medication-Related Osteonecrosis of the Jaw.
A 75-year old male patient received 4 mg zolendronic acid iv every month between XI 2018 – X 2019 as a treatment for prostate cancer

A. Multifocally exposed bone and purulence observed in the region of the left body of the mandible; the possible cause of MRONJ occurrence was unfitting partial denture in mandibula
B. Cone beam computed tomography showed excessive osteolysis in mandibular alveolar bone area

photo source: author's own materials



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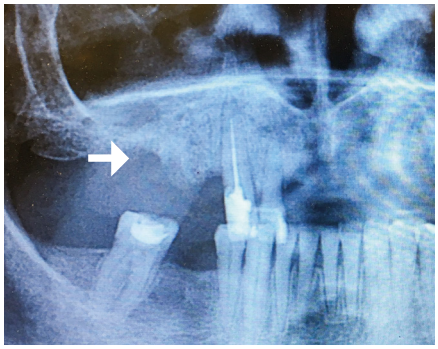

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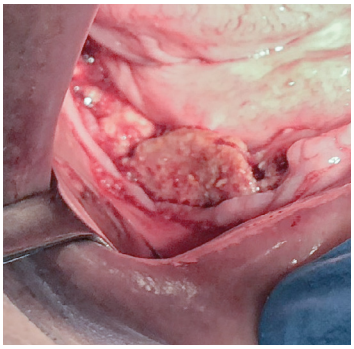

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Figure 2. Example of Medication-Related Osteonecrosis of the Jaw. A 64-year old female patient received 4mg zolendronic acid iv every month between X 2017 – X 2019 as a treatment of breast cancer metastases

A. Exposed bone was observed in the region corresponding to tooth 14-15; the possible cause of MRONJ occurence was extraction of tooth 15 and following wear of unfitted partial denture. B. Panoramic radiography disclosed alveolar bone loss in region corresponding to teeth 14-15.

photo source: author's own materials

Figure 3. Example of Medication-Related Osteonecrosis of the Jaw. A male patient received 4mg zolendronic acid as a adjuvant treatment of multiple myeloma Exposed bone was observed in the right side of the mandibula; the possible cause of MRONJ occurence was extraction of teeth in above mentioned area.

Table 1. Treatment strategies according to the severity of MRONJ (modified from the 2014 AAOMS Guidelines)

MRONJ STAGE	CLINICAL PICTURE	TREATMENT
0	Tooth or jaw pain without a clinically noticeable cause, tooth movement without a clinically noticeable cause	• Systemic treatment (antibiotics and analgesia), • Referral to a dentist and follow-up visits every 8 weeks, • Patient education
I	Asymptomatic focal bone necrosis without inflammation	• Antibacterial mouthwash, • Follow-up visits every 8 weeks, • Patient education
II	Focal bone necrosis with symptoms of inflammation and significant pain	• Systemic treatment (antibiotics and analgesia), • Bone debridement to control the infection and to reduce trauma from sharp bone fragments, • Antibacterial mouthwash, • Follow-up visits every 8 weeks, • Patient education
III	Focal bone necrosis with symptoms of inflammation and significant pain and excessive osteonecrosis of the jaw bones	• Systemic treatment (antibiotics and analgesia), • Surgical debridement or resection of the necrotic bone, • Antibacterial mouthwash, • Follow-up visits every 8 weeks, • Patient education

re osteoclast recruitment, reduction of osteoclast activity by inducing their apoptosis [6, 8]. Thanks to their ability to bind with the bone matrix, the therapeutic effect of bisphosphonates may last up to 10 years after discontinuation of doses [4, 8]. Low-dose (oral) bisphosphonates such as alendronic acid, ibandronic acid and risedronic acid are used in majority of their indications described above [6]. However, ibandronic acid, pamidronic acid and zolendronic acid may also be administered intravenously (iv) once every 3 months and once a year, respectively, to treat the same illnesses. High doses of iv bisphosphonates, such as ibandronic acid, pamidronic acid and zoledronic acid are most commonly administered for prevention of metastasis to the bones in the course of multiple myeloma or cancer of the breast, lungs and prostate [4, 6, 8].

Denosumab is a human monoclonal IgG2 antibody which inhibits the activation of osteoclasts and their precursors by selectively binding the receptor activator of nuclear factor k-B ligand (RANKL) on their surfaces [12]. This results in inhibition of maturation, function and longevity of osteoclasts, thus reducing bone resorption [2, 6]. Unlike bisphosphonates, denosumab does not bind with the bone matrix, thus its effect is minimal 12-24 months after discontinuation [8]. Low doses of denosumab are indicated for osteoporosis and prevention of bone metastasis (subcutaneous every 6 months), whereas high doses are administered for the treatment of bone metastases (subcutaneous every 4 weeks) [6].

Angiogenesis inhibitors are indicated in cancer treatment where they limit tumor and metastasis growth [8, 13]. Of all the drugs in this group, anti-VEGF (vascular endothelial growth factor) and TKI (tyrosine kinase inhibitor) seem to correlate with higher risk of MRONJ [14-16]. Similarly to denosumab, angiogenesis inhibitors do not bind with bone matrix and are metabolized up to 20 days after discontinuation [6-7].

Discussion

Prevention of MRONJ should be based on qualification of patients to their appropriate MRONJ risk group, assessment of possible additional risk factors and formulating individual treatment recommendations [7]. Drug dose, duration of treatment and presence of additional MRONJ risk factors determine the patient's risk of MRONJ [6] [Table 2].

Up to 90% of MRONJ cases occur in oncological patients treated with high-dose antiresorptive drugs [6]. Osteonecrosis is usually caused by a local oral infection or injury of mucosa or bone [6-7]. The most common risk factor related to the oral cavity is tooth extraction (45-61%), periodontal disease (10%) and poorly fitted dentures [3, 7, 17-18] [Table 3]. That is why cooperation between physicians and dentists is crucial in successful prevention of MRONJ [19-21]. Literature points out that MRONJ risk is lower among patients who were referred to a dentist and preventive procedures were performed [6, 22-23].

Table 2. Risk group assessment

RISK GROUP	TREATMENT	DURATION OF TREATMENT	RISK FACTORS PRESENT?*
LOW RISK OF MRONJ	**LOW-DOSE** • low doses of oral bisphosphonates • Denosumab 60 mg every 6 months	Treatment < 3 years	No
HIGH RISK OF MRONJ	**LOW-DOSE** • low doses of oral bisphosphonates • Denosumab 60 mg every 6 months	Treatment > 3 years	Yes
HIGH RISK OF MRONJ	**HIGH-DOSE** • high doses of bisphosphonates iv • Denosumab 120 mg every 4 weeks	Irrelevant	Yes

*** MRONJ risk factor: antiresorptive drugs, corticosteroids, chemotherapy, poor oral hygiene, periodontal disease, poorly fitted dentures, cigarette smoking, comorbidities (cancer, hematologic disease, immune system diseases, diabetes, anemia)**

Table 3. MRONJ local risk factors (according to AAOMS 2014)

DENTAL	SURGICAL	ANATOMICAL
• **Periodontal disease** • **Peri-implantitis** • **Poorly fitted dentures**	• Tooth extractions • Dental implants • Endodontic or periodontal procedures • Bone regeneration procedures	• Bone exostoses • Torus mandibularis • Mylohyoid line • Torus palatinus

The specific preventive measures are dictated by assessing the patient's risk of MRONJ and by the stage of treatment with antiresorptive drugs [6, 21, 23]. Regardless of their MRONJ risk, all patients should be examined by a dentist and instructed about oral cavity hygiene [5-6, 19, 24]. In addition, the dentist should perform oral cavity sanation, perform periodontal treatment and check if the patient's dentures fit properly. The patient should be informed about the symptoms of MRONJ and the necessity of reporting them early [6].

After starting therapy with angiogenesis inhibitors or antiresorptive drugs, low-risk patients may undergo required and/or recommended dental treatment [5-7, 19, 24].

A different approach is required for patients with high risk of MRONJ. A dental consultation is recommended before any surgical, periodontal or dental implant procedure. Information from the physician supervising the antiresorptive drug therapy is also required [6, 21].

Literature suggests that lack of cooperation between physicians and dentists is correlated with a higher incidence of MRONJ [25]. Dentists may be the first doctors who diagnose signs of MRONJ, and patients with such diagnosis need to be referred to a maxillofacial surgery center for specialized treatment [23]. Regardless of their risk of MRONJ, patients treated with antiresorptive drugs need to complete dental hygiene training and have a follow-up visit every 4 months [7].

Conclusions

Increased incidence of MRONJ forces a multi-disciplinary cooperation between dentists and the physicians who are treating the underlying illness. The dentist may be the first doctor who diagnoses signs of MRONJ and initiates treatment, thus increasing the likelihood of good outcome. Currently there is no defined MRONJ treatment algorithm, so it is critical to implement preventive measures before starting antiresorptive drug treatment. Patients who are qualified for treatment with angiogenesis inhibitors or antiresorptive drugs should undergo dental examination and undergo full oral sanation in order to reduce the risk of complications.

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REVIEW ARTICLE

Thoracic trauma – principals of surgical management

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Abstract

Thoracic trauma continues to be a significant surgical problem. It is estimated that 25% of trauma-related deaths are due to penetrating and blunt thoracic injuries. Principals of surgical management of specific thoracic injuries like: tension pneumothorax, open pneumothorax, massive haemothorax, flail chest, cardiac injuries, ruptures of the aorta, tracheobronchial tree lesions, oesophageal and diaphragmatic injuries have been reviewed. Awareness of the potential for deterioration and early correct identification of life threatening thoracic injuries are the keys to successful management. Good outcomes in the management of thoracic injuries depend on rapid transport of the injured patient to the hospital, effective diagnostic and therapeutic measures and an aggressive involvement of an experienced surgical team, optimally in the operating theatre. Successful management of these injuries depends on effective prioritisation of procedures based on the ABC principals combined with a rapid diagnosis of severe injuries and aggressive surgical treatment of life-threatening lesions following penetrating and blunt trauma. Rapid decompression of tension pneumothorax and emergency thoracotomy, especially in patients following penetrating thoracic trauma may result in good outcomes. Effective management of severe thoracic injuries requires an integrated approach and cooperation of a multidisciplinary trauma team, including experienced thoracic and cardiac surgeons.

Keywords: penetrating · blunt · thoracic · trauma · surgery

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Overview of thoratic trauma

Thoracic trauma constitutes to be a significant medical problem and a major challenge for surgeons. It is estimated that 25% of road traffic accident-related deaths are due to thoracic lesions. Many of these patients die immediately at the scene because of rapid exsanguination secondary to rupture of the aorta or major vessels. Some patients die later as a consequence of acute respiratory distress syndrome (ARDS), multiple organ failure (MOF) and sepsis [1-2]. Lung is a very sensitive target organ for secondary injury fol-

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lowing shock and remote tissue alterations. Tissue damage and shock can activate an inflammatory cascade which contributes to pulmonary insufficiency. Patients who reach hospital sometimes die as a consequence of misassessment, delay in treatment and other inadequacies; these are preventable deaths. It was found that a significant percent of in-hospital deaths from thoracic trauma were preventable, with injuries either not being recognized, diagnosed with delay or being inadequately treated [1, 3].

Thoracic trauma is quite frequent in Poland. In a large study from Poland, thoracic injuries were diagnosed in about 25% of 681 lethally-injured patients who were treated at a university trauma department [1]. These injuries were found as isolated chest lesions or components of multiple injuries localized in different anatomical regions and contributing significantly to the mortality [1]. Other studies suggest that 50% of patients who died in the pre-hospital phase had severe thoracic injuries. Severe vascular lacerations causing massive haemorrhage to pleural cavities and mediastinum were combined with vast injuries of the abdominal organs, brain and bone fractures [2-3].

Treatment challenges

Successful treatment of thoracic trauma continues to be challenging. It depends on optimal and effective prioritization of management based on the principals of ABC, with a rapid identification of severe injuries and aggressive surgical treatment of life-threatening injuries [4].

Thoracic injuries are usually classified as penetrating or blunt, the latter encompassing direct trauma as well as crush, acceleration or deceleration and blast injuries. In patients with polytrauma, life-threatening injuries that are without obvious external signs may be missed as attention is paid to more visible but less clinically serious injuries. Penetrating trauma may cause pneumothorax or haemothorax with massive blood loss. Some patients after chest trauma deteriorate rapidly. But on the other hand, with proper management they can rapidly improve. In patients with penetrating injuries surgical operations are frequently indicated, while diagnostic investigations are less required than in blunt trauma. In some cases, the distinction between blunt and penetrating thoracic trauma should be based on high index of suspicion because penetrating injuries often coexist with severe blunt injuries of solid organs and major vessels [4].

Careful analysis of patterns and mechanisms of chest injuries may be helpful in some situations. It has been proven that:

A) penetrating thoracic trauma is usually connected with laceration of the heart, major vessels, intercostal vessels, airways, lung, oesophagus and diaphragm; there is also a risk of trauma to adjacent organs in the abdominal cavity (spleen, liver) and retroperitoneal space (major vessels, kidneys) [5],
B) blunt thoracic trauma may cause cardiac contusion, lung contusion, rib fractures, thoracic spine fractures,
C) crush mechanism may cause rupture of bronchus, oesophagus, heart, lung contusion, rib fractures with or without flail chest ,
D) deceleration thoracic trauma may cause aortic rupture, airway damage, diaphragmatic rupture,
E) blast mechanism may be responsible for disruption of any intrathoracic organ and vessel.

Regardless of its mechanism and pattern, the main consequence of thoracic trauma is reduction of vital functions such as respiration and circulation, leading to hypoxia, hypovolaemia, reduced cardiac output. The sequelae of this injury have a detrimental effect on organs beyond the chest cavity, e.g. kidneys, liver, brain, gastro-intestinal tract.

In Poland, penetrating thoracic trauma is most often the result of knife injury. Knife wounds usually are connected with low velocity penetration and mortality is strictly related to the injured organ [1]. Compared with other countries, the occurrence of firearm-related penetrating injuries in Poland is sporadic. Firearm injuries cause more extensive tissue destruction related to the kinetic energy. Bullets are designed so that on impact, the missile expands or shatters, imparting all its energy to the tissue. Other ballistic characteristics of the bullet may contribute to tissue damage e.g. yaw, tumble and pitch. Tumbling may be important in high-velocity weapons, i.e. over 800m/s. Shotgun blasts are very dangerous because all of the energy is transferred to the tissue [4].

Patients with penetrating thoracic injuries to the mid-torso require an aggressive surgical approach, especially those with anterior wounds. If the wound does not obviously penetrate the abdomen, an option is to explore the wound under local anaesthesia whether or not it has penetrated the peritoneal cavity or retroperitoneal space. If peritoneal penetration has occurred, laparotomy is mandatory in order to find all possible injuries. For stable patients following thoracic trauma, options include other diagnostic measures like thoracoscopy and laparoscopy [6].

Patients following chest trauma arrive to hospitals in two physiological states: haemodynamically unstable or haemodynamically stable. The state of the

patient determines the specific diagnostic and therapeutic approach. The initial assessment of any injured patient must place priority on the evaluation of the airway and the adequacy of the cardiovascular system according to the ABC algorithm. A rapid physical examination will determine if the patient is cyanotic, tachypneic or has other problems with respiration. In the patient with a penetrating or a blunt injury to the upper torso who is unstable, most probably haemorrhage is occurring into the chest cavity; the patient should be taken to the hospital with no delay. It is important to insert a chest tube as soon as possible (through the 4-th or 5-th intercostal space) during the initial assessment and resuscitation in the emergency department. Bilateral chest tubes may be indicated. A chest x-ray is not required to insert a chest tube, but it is useful to do in order to confirm tube placement [7-8].

FAST or CT

Focused Assessment with Sonography for Trauma (FAST) has been widely used in trauma centers and emergency departments. It is a rapid, non-invasive, ultrasound diagnostic protocol used both in hamodynamically unstable and stable patients with penetrating or blunt injuries. It is usually performed in the resuscitation area of the Emergency Department. The extended FAST protocol (eFAST) may be very valuable in identifying cardiac tamponade, haemothorax and haemoperitoneum [2, 4]. In patients who are haemodynamically stable, a plain anteroposterior (AP) chest radiograph is still a gold diagnostic standard to identify pneumothorax or haemothorax. The eFAST examination should be performed within 10 minutes since the patient's arrival at the emergency department. A thoracic radiograph before placement of a chest tube may be helpful in excluding rupture of a diaphragm with possible herniation of a stomach or intestines to the pleural cavity, especially in patients following blunt trauma. Clinical signs in patients with chest injuries sometimes are subtle or misleading. Therefore, the thoracic radiograph helps to identify important lesions which require emergency surgical intervention or may suggest further investigations such as: CT scan, FAST, Transoesophageal Echocardiography (TEE) or thoracoscopy and laparoscopy [9-11].

Whole body computerized tomography (WBCT, also referred to as polytrauma scan) is a widely accepted diagnostic tool in the primary management of patients following major trauma. In many institutions WBCT is indicated even when the patient is haemodynamically unstable, as it may identify severe injuries within minutes [12]. WBCT is particularly recommended in patients after blunt trauma and with suspected multiple injuries, as it can reveal occult thoracic lesions [11].

Specific thoracic injuries

Management of specific thoracic injuries depends on the state of a patient arriving to the emergency department. Clinically, thoracic injuries are divided into two types: immediately life-threatening and potentially life-threatening (see Table 1).

Table 1. Thoracic injuries divided by their urgency

Immediately life-threatening injuries	Potentially life-threatening injuries
• airway obstruction combined with facial bone and soft tissue damage, • tension pneumothorax, • open pneumothorax, • flail chest, • massive haemothorax causing impaired circulation, • cardiac injuries, • traumatic rupture of the aorta (TRA), • air embolism.	• myocardial contusion, • pulmonary contusion, • traumatic diaphragmatic herniatiom (TDH), • tracheobronchial tree disruption, • simple haemothorax, • simple pneumothorax, • oesophageal disruption

Immediately life-threating injuries

It is critical to identify and treat airway obstruction as soon as possible during the primary survey at the Emergency Department. Tension pneumothorax causes a real threat to life because of the progressive build-up of air within the pleural cavity, caused by one-way leak from a lacerated lung, airway or a chest wall. Air enters the pleural space on inspiration, but cannot be evacuated during expiration due to the functioning of one-way flap valve. This creates progressive accumulation of air with collapse of the ipsilateral lung, causing severe hypoxia, shift of the mediastinum to the opposite side, compression of the contralateral lung with atelectasis and decreasing venous return to the heart. The combination of hypoxia, impaired ventilation and

critically reduced cardiac output leads to traumatic cardiac arrest unless the tension is decompressed. Tension pneumothorax can complicate both penetrating and blunt trauma. It may be also induced iatrogenically during the insertion of central venous lines or by the incorrect application of occlusive dressings to penetrating chest wall wounds. It should be remembered that tension pneumothorax may be intitiated in patients with a simple pneumothorax who are put on positive pressure ventilation. Awareness of this potential for the deterioration and early identification and treatment are the key to effective management. Diagnosis of a tension pneumothorax should be based on physical examination and radiological examinations should not be performed [3, 7]. The diagnosis can be difficult in a noisy emergency department. The classic signs are connected with decreased or lack of breath sounds and percussion tympany on the ipsilateral side, tracheal and cardiac deviation to the contralateral side, reduced chest movements, elevated venous pressure, progressive tachycardia, hypotension with *pulsus paradoxus*. When untreated, this pathology leads to full circulatory collapse and cardiac arrest with pulseless electrical activity (PEA). In rare cases tension pneumthorax may be bilateral.

Tension pneumothorax

Tension pneumothorax is the most frequent reversible cause of death during resuscitation of patients in pre-hospital traumatic cardiac arrest [13]. In the patient who is dying there should be no hesitation in performing immediate decompression of the affected side, converting tension pneumothorax into an open pneumothorax or simple pneumothorax [7-8]. In emergency the decompression is achieved by insertion of a dedicated needle (or a large–caliber, e.g. ~16 gauge intravenous catheter) into the fifth intercostal space in the anterior axillary line. The hiss of air usually confirms decompression and clinical improvement should be noticed. The cannula should be left open (resulting in an open pneumothorax) and the next step is to insert a chest tube, followed by re-examination of the chest and an AP chest radiograph. It must be remembered that a needle thoracostomy can easily become kinked or displaced, allowing the tension pneumothorax to recur. One should also keep in mind that the inserted drain may be blocked. It is obvious that these patients need careful clinical monitoring and repeated clinical examination [4, 13].

Massive haemothorax

Massive haemothorax is another life-threatening condition. Intercostal and internal mammary vessels are commonly disrupted. It should be remembered that each hemithorax can hold up to 3 l. of blood. It is estimated that approximately 50% of patients with hilar, great vessel or cardiac wounds die immediately after the injury, while about 25 % survive for about 5-6 minutes; these are pre-hospital deaths. The remaining 25% arrive at the Emergency Department alive and require immediate diagnosis and surgical treatment. The diagnosis of massive haemothorax is invariably made by the presence of shock, respiratory insufficiency and deviation of the mediastinum. Patients in shock and with respiratory insufficiency must be intubated with no delay. A chest radiogram may confirm also the amount of blood loss. A chest tube should be inserted in order to relieve the threat of ventilatory embarrassment. The main objective in the treatment of massive haemothorax is to restore blood volume, treating actively shock together with drainage of the haemothorax via an intercostally inserted chest tube. In majortity of the patients with haemothorax the proper placement of a chest tube allows for effective evacuation of the blood. However, if initial drainage of blood is > 1500 ml or ongoing drainage is > 200 ml/h for about 4 or more hours, then thoracotomy in the surgical theatre is likely to be required. Ongoing bleeding, patient's clinical status and requirement for blood transfusion are important parameters that should be taken into consideration deciding about the need for the thoracotomy. In the operated patients major vessels, intercostal arteries, injury to the hilum of the lung or to the myocardium are the main sources of massive bleeding. These injuries should be treated by oversewing the lesion, making sure that bleeding is controlled [7-8]. In some instances resection of the lung segment or lobe and even pneumonectomy may be necessary [3, 14].

Injuries of the chest wall are common in patients following blunt trauma causing multiple fractures both in anterior and posterior parts of the ribs. When the chest wall loses its bony stability within thoracic cage, it becomes flail and starts to move paradoxically. The flail segment is moving in the direction opposite to the stable chest wall during inspiration and expiration. In many patients multiple rib fractures are accompanied by significant blood loss and lung contusion. Diagnosis of flail chest is based on clinical examination. In patients with flail chest, severe pulmonary contusion contributes to respiratory insufficiency. Treatment is usually initiated with high flow oxygen and lung expansion by intermittent positive pressure ventilation. Intercostal chest tubes are almost always necessary, particularly if positive pressure ventilation is needed. The aim of further management is to preserve respiratory function. In all patients effective pain relief is required, in some cases epidural anaesthesia may be very effective. Careful fluid management is indicated

because injured lungs are extremely sensitive to inadequate perfusion and to fluid overload. In cases with respiratory distress and hypoxia due to the flail segment, endotracheal intubation and mechanical ventilation are necessary, particularly in patients with large pulmonary contusion. Currently, there is an increasing tendency to concentrate on the associated damage to the underlying lung in the form of pulmonary contusion and ARDS [15]. Internal stabilization by means of endotracheal intubation and mechanical ventilation are effective therapeutic options in patients with bilateral multiple rib fractures. Some patients with unilateral flail chest can be managed selectively with ventilatory assistance or with short term use of mechanical ventilation. It is imperative that these patients have vigorous pulmonary care (aggressive pulmonary hygiene and cough-deep breathing) and are treated in departments by experienced and skilled medical staff.

It should be remembered that rib fractures are independent predictors of other abdominal solid organ injuries (spleen, liver) [16]. Currently, operative reduction and fixation (ORIF) of the chest wall has been evolving as a method of chest wall stabilization [17]. ORIF of broken ribs may be performed in adult patients with flail chest with measured metal plates, bracketed fixators or resorbable plates. This approach improves primary and secondary outcomes in appropriately selected patients [18].

Penetrating heart wounds

Penetrating heart wounds represent some of the most extreme emergencies that a physician must manage. A penetrating cardiac trauma creates several rapid life threatening sequelae that include massive haemorrhage, cardiac tamponade and myocardial injury [19]. The period between trauma and successful therapeutic measures very often is dramatically short. More effective emergency medical response systems have resulted in more opportunities to treat these severely injured patients at the hospital. It is estimated that at least about 50% of patients with a penetrating cardiac injury may reach the trauma unit alive with an opportunity to be treated and finally salvaged.

Whatever the cause of penetrating injuries to the heart, a series of events occurs that can compromise cardiac function and quickly cause death unless timely interventions are instituted. The first problem is the penetration of a cardiac chamber, which leads to bleeding. If a large damage to the pericardium is made, bleeding into either chest cavity or mediastinum may occur; thus hypovolaemic shock may occur without cardiac tamponade. If the pericardial damage is small or seals itself, cardiac tamponade may develop with physical signs of hypotension, distended neck veins and muffled heart sounds (Beck's triad). In such a situation, a small amount of blood in the pericardial space can cause serious cardiovascular instability by restricted venous return and thus "choking" the heart. In other cases, cardiac trauma may cause damage of the cardiac valves or ventricular septum and may lead to uncontrollable heart failure. The pericardial sac does not acutely distend; 75-100 ml of blood can produce a life-threatening tamponade in the adult. The classic Beck's triad is not always seen in the Emergency Department; neck veins may not be distended in deep hypovolaemia and muffled heart sounds can be difficult to identify in noisy surroundings.

It seems that penetrating cardiac injuries should be easy to diagnose. In reality it happens that such an injury may be overlooked, especially in fully-clothed, drunk or unconscious patients with other coexisting lesions. Therefore, it is imperative that all members of the emergency services and surgeons should treat these patients with a high degree of suspicion starting from the scene of the trauma. The patient should be taken to the hospital as soon as possible according to the "scoop and run" (or "load and go") approach and immediate emergency thoracotomy should be initiated [20-21]. Ideally an emergency thoracotomy should be performed in the operating theatre, however if the patient is *in extremis*, this life-saving procedure can be performed in an Emergency Department. A left anterolateral thoracotomy through the 4-th or 5-th intercostal space and long pericardial incision anterior to the phrenic nerve allows good exposure of the heart for control of haemorrhage and provides the optimal access for direct compressions of the heart during resuscitation. This surgical access is made in the supine position of a patient and may be extended across the sternum into the contralateral hemithorax (the "clamshell" incision or bilateral thoracotomy). Majority of cardiac wounds can be surgically closed with simple sutures or horizontal mattress sutures of a 3/0 or 4/0 monofilament. Bolstering the sutures with Teflon pledgets may be required. Care must be taken not to suture coronary vessels. Loose approximating sutures of the pericardium after the injury is repaired prevent from a serious complication connected with the cardiac herniation through the pericardium, which may occlude venous return and cause sudden death. In case of damage to the valves, chordae tendineae, septum or myocardium, further cardiac surgery may be needed.

Tears of the aorta or pulmonary arteries

Tears of the aorta or pulmonary arteries are associated with blunt or rapid deceleration mechanism such as falls from significant height, high speed motor vehicle crashes. The aorta may be transected comple-

tely or partially. The most common site of rupture is at the attachment of the *ligamentum arteriosum*. It is estimated that aortic rupture is immediately fatal in about 85-90% and accounts for 15-20% of immediate overall trauma deaths due to road traffic accidents. The immediate survival of the patient depends on the development of a contained haematoma, maintained by the intact *adventitia*. The survival of the patient after reaching the hospital depends on early diagnosis followed by effective treatment. Any suspicion of an aortic injury necessitates further rapid investigation. A widened mediastinum over 8 cm at the level of aortic arch is the most consistent finding on a chest radiogram. Contrast-enhanced spiral CT scan has become the investigation of choice for the proper diagnosis of aortic injuries with sensitivity and specificity approaching 100%. When this lesion is suspected, intended permissive hypotension should reduce the risk of a rupture of the adventitial layer containing the tear. The goal for systolic blood pressure should be approximately 90-100 mm Hg. Alpha and β blockade (e.g. esmolol, labetolol, nitropusside) should be instituted after significant bleeding from other injuries has been excluded. Currently the treatment of traumatic rupture of the aorta has evolved from performing emergent open surgical repair with clamping and sewing technique to minimally invasive treatment by means of interventional radiologic technique with the interposition of a vascular intra-aortic stent graft [22-23].

Potentially life-threatening injuries

Most patients with major tracheobronchial tree and airway injuries die at the scene as a result of asphyxia. Those who survive to reach the hospital are usually *in extremis*. These lesions are suggested by massive haematoptysis, airway obstruction, progressive mediastinal air, subcutaneous emphysema, significant persistent air leak after placement of a chest tube. In most cases the air leak stops after a few days (combined with good expansion of the lung) with the chest tube drainage alone. If there is a persistent leak of air for a long time, thoracic CT and bronchoscopy are indicated to detect the damage. In case of damage to the trachea or bronchus, a posterolatertal thoracotomy is needed. Definitive treatment includes primary repair with absorbable sutures. It should be remembered that chest drainage is required in case of any pneumothorax [24].

Diaphragmatic injuries

Diaphragmatic injuries occur in patients following violent abdominal and thoracic compression mechanism. The left diaphragm is injured 6 times more frequently than the right one. The diaphragm normally rises to the fifth intercostal space during normal expiration, so that any patient after mid–torso trauma is at risk for diaphragmatic rupture. Right-sided lesion may show only a raised hemidiaphragm, whereas a left-sided may show herniation of the stomach, spleen and intestines. Accurate diagnosis is obtained optimally on thoraco-abdominal CT or NMR. All diaphragmatic ruptures should be repaired. Those injuries that are not repaired will present later, usually with dangerous incarceration of the small bowel, colon or omentum into the hernial defect. Acute repair may be accomplished via laparotomy or thoracotomy. The preferred surgical closure of diaphragmatic ruptures is based on interrupted sutures. In large defects synthetic prosthetic material or flaps should be used [25-26].

Oesophageal injuries

Oesophageal injuries are usually caused by penetrating trauma. The diagnosis is also probable in patients after blunt trauma with pneumothorax or haemothorax in the absence of rib fractures. On chest X-ray, patients may present posterior mediastinitis with fever, pain and persistent pneumothorax. Once diagnosed, posterolateral thoracotomy and routine surgical closure should be performed. Injuries to the oesophagus should be surgically repaired if the injury is less than 6 hours ”old”. It is important to put the sutures in situ in order to avoid damage to the vasculature of the oesophagus. In “older” oesophageal injuries wide drainage with chest tubes, diverting oesophagostomy and nutritional support by feeding gastrostomy may provide the optimal management [4].

Strict criteria for emergency department thoracotomy (EDT) (historically called “emergency room thoracotomy”) remain controversial. Overall survival rates for patients undergoing ED thoracotomy vary from 4 to 33% across numerous studies [27-28]. This procedure should be reserved to control haemorrhage, to control the aortic outflow (aortic “cross-clamping”) and to perform direct cardiac compressions. There should be no hesitation to perform EDT in patients with cardiac arrest after penetrating trauma. EDT must be initiated only in intubated patients. It should be also started if only pulseless electrical activity (PEA) has been recorded. EDT has been found most effective in penetrating cardiac wounds, especially when cardiac tamponade is present and in those patients in whom there has been a witnessed post traumatic cardiac arrest [29]. The most common surgical access for this procedure is through the 4-th or 5-th left intercostal space. The incision when needed may be extended to the opposite side (“clamshell” incision) providing good access to the

heart, mediastinum and both pleural cavities. Median sternotomy gives excellent exposure to the heart and great vessels. EDT is contraindicated when there has been ineffective cardiopulmonary resuscitation (CPR) for more than 10 minutes with or without endotracheal intubation and in cases, when there were no signs of life at the scene. EDT is a team event. This procedure should be terminated if irrepairable cardiac damage has occurred, pulseless electrical activity (PEA) and asystolic cardiac arrest have occurred for over 10 minutes.

The survival rate in patients following EDT after penetrating thoracic trauma is about 10%, but it has been found beneficial in around 50% in patients presenting with signs of life after isolated penetrating cardiac injuries and only rarely in those presenting without signs of life (below 2%). In non-cardiac penetrating wounds the survival rate is around 25% when signs of life were noticed. Only 1-2% of patients after EDT are salvaged after blunt trauma regardless their clinical status on admission. However, a patient after blunt trauma who is exsanguinating via a chest tube due to ruptured thoracic vessels may be salvageable with EDT. Whatever the indication, EDT should be performed by an experienced surgeon, optimally in the operating theatre with good lighting, appropriate instruments and a functioning suction apparatus. It must be noticed that there is an extremely high mortality rate associated with all thoracotomies performed anywhere outside the operating theatre, especially when performed by non-surgeons [7, 29]. A candidate for an EDT should be by all means transported as soon as possible to the trauma center or to a surgical department providing professional trauma surgical approach [30-31].

Effective management of severe thoracic injuries demands integrated approach and necessity of cooperation of a multidisciplinary trauma team or an extended trauma team with the participation of experienced thoracic and cardiac surgeons.

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REVIEW ARTICLE

How to write a scientific paper? Lessons from a distinguished scientist and editor

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Abstract

This article is an instructive guide on how to write and publish a scientific article. It was inspired by a lecture given at the Medical University of Gdańsk by a distinguished professor. To further advance science, particularly in the currently emerging era of individualized medicine, the collaboration of researchers with a varied level of experience and from different areas of expertise is needed. It is vital to publish the results of research quickly and effectively. Knowing the basic mechanisms of writing and publishing will help to disseminate research results more effectively.

Keywords: neuroscience · publishing · scientists · neurology · neurosurgery · generations

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This article is an instructive guide on scientific writing and successful publication. It was inspired by professor Zbigniew Wszołek's keynote lecture (presented on May 28, 2019 at the Medical University of Gdańsk) on the subject *How to write and publish a scientific paper?*

How to start writing?

When writing the manuscript, one may choose to write in the following order: results, methods and materials, introduction, discussion, conclusion and the abstract. In this way, the author is 'forced' to analyze

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all the data for any significant findings and to formulate the main thesis of the paper before doing most of the writing. However, the final version needs to follow the universally-accepted structure: first the abstract, then the introduction, materials and methods, results, discussion, and last but not least the conclusion.

Authorship

If two authors contributed equally to a publication, they may feel free to share first authorship [1]. In 2012 almost 30% of all medical publications had co-first authorship [2]. For instance, this editorial shares first-authorship between the three authors. Placing the most senior investigator as the last author is customary, however according to the current guidelines if the senior investigator's role consisted of project supervision only, then s/he should be just mentioned in the acknowledgement section [3]. Group authorship (Group Corporate Authorship) instead of single authors is a possibility and is recognized by the National Library of Medicine database [4].

The Abstract

The abstract is a crucial part of a manuscript because it provides the initial impression for the reader. Scientific journals require that the abstract is limited to about 200 to 300 words and is a separate part of the manuscript. The most significant and most important parts of the paper are usually presented in the abstract. It is typically arranged in the following sections: background, aim/purpose, material and methods, results and conclusion.

The Introduction

The introduction is a short and concise review of your topic and is directly relevant to the aim of your study. It follows a standard format and should not be longer than three paragraphs. The first paragraph focuses on information that is already known and established. The second paragraph introduces the knowledge gap or the limitations of current scientific knowledge. The third paragraph declares the purpose of the study and why the study may be clinically relevant. Notably, the introduction should not yet answer the main research question and should not contain any results.

Ethical Commitee Approval & Patient Consent

Ethical committee approval and patient consent is required for almost any study involving people or their information (e.g. responses on questionnaires). Obtaining approval may take several months so we recommend starting this process early. Only data that is publicly available (such as online information from the World Health Organization) does not require official approval for use in research. If author/s have any specific questions or concerns particularly related to the obtaining permissions for publication, it is advisable they seek the guidance of the local Ethics Committee.

The Material and Methods

This section is a detailed description of how the material was obtained and what test or experiments were performed. There should be enough details mentioned to make it possible to replicate the described study. It is often helpful to divide this section with headings (e.g. inclusion criteria, exclusion criteria, experimental protocol and statistical methods). Instead of writing detailed descriptions of commonly used methods or protocols, authors may simply cite a previous study that involved the same methods. Flowchart diagrams may be useful for describing complex study designs.

The Results

This section summarizes the data with significant relationships and the overall trends and may be supported by tables or graphs. Like the material and methods section, when necessary the results section may be divided into subsections with headings. Only the most important data should be repeated from the tables and should be analyzed when possible (e.g. the percentage change instead of absolute values). In this section, the term "significant" should be only used to mean "statistically significant." Analysis of your data should be reserved for the discussion section. All data should be presented, including non-significant findings and negative results. We recommend making one's findings as transparent as possible by providing supplementary raw data as it may encourage confidence in a reader [5]. Avoid making the common mistake which is mixing the results with the methods and materials.

The Discussion

The discussion consists of six basic parts: the key findings, context, limitations, future outlook, clinical implications and the conclusion.

1. The key findings state what the data means and if the findings are novel. This information should be summarized to the extent that even a non-expert

may understand the relevance of the findings to to health and/or science.
2. In the context section, the authors compare their results with the most recent scientific literature. This section should explicitly state whether your findings confirm or challenge the current paradigm. Here, you may discuss the results or offer possible mechanisms for your findings.
3. The limitations section is obligatory and is a chance for the author(s) to respond to the criticism that they anticipate from the peer-reviewers and of course the readers. This section should convince the reader that despite their limitations, your results are relevant.
4. In the future outlook section, the authors may recommend confirmatory studies and suggest the direction/s of follow-up studies.
5. The clinical implications section outlines the impact that the research results may have on clinical practice. In other words, answer the question "why should physicians pay attention to the findings of the paper?"
6. The conclusion is where the main findings are emphasized and the final message is restated.

Citations

Every publisher aims to increase the impact factor of its journals (which is measured by the number of citations a journal obtains over the last few years) [6]. Thus, it is in the interest of the author to cite papers published in the journal they are sending their manuscript to.

Plagiarism

We encourage authors to check for plagiarism before submitting a manuscript. Quoting other papers is fine, however, to help you and your co-authors distinguish it from your original text we recommend placing it in bold or italics. Auto-plagiarism, a situation when an author copies his/her fragment from a previously published article, is also prohibited.

Language

We recommend that a researcher not pay excessive attention to the language, style and grammar for the first draft. In the first draft the goal is to write the main, technical/scientific content of the paper, whereas the grammatical and stylistic improvements should be left for later revisions. To improve the writing, we suggest regularly reading scientific journals relevant to one's own research interest in order to become familiar with the correct and accepted vocabulary, phrasing and sentence structure. We recommend authors whose native language is not English to avoid direct translations from their native language to English because this often results in confusing or awkward phrases and incorrect sentence structure.

Revise the manuscript several times before final submission, with the intention of making technical topics easy to understand and pleasant to read even for non-experts. The manuscript's final version should contain convincing arguments with no grammatical mistakes. When expressing opinion/s, authors should remain professional, polite, fair and avoid emotionally-charged words and phrases.

Choosing the Journal

When choosing the journal to submit your manuscript, keep in mind not only its impact factor but its scope (e.g. a paper on stroke treatment should not be sent to a movement disorders journal). We recommend browsing the latest issue of a journal to gain an understanding of what types of articles are actually published there.

The Submission Process

We encourage authors to identify their target journal before they start writing their paper so that they are aware of the author guidelines. These provide information about the word limit, number and format of the tables or figures, style of references, conflict of interest forms, et cetera. A manuscript may be rejected at the initial submission stage if it does not meet the journal's requirements, therefore adhering to these guidelines is one of the keys to successful publishing. After you submit your manuscript on the journal's online system the following outcomes are possible: accepted; accepted pending/with minor revisions; accepted pending/with major revisions; rejected but re-submission possible; rejected with no resubmission possible. Most papers will require some revisions, more about that later.

The Cover Letter

The cover letter is often an unappreciated part of one's submission as it offers the opportunity to tell the Editor something that cannot be stated in the manuscript. If it is well-written, it may help convince the Editors to publish the manuscript. However, a well-written cover letter will not 'save' a poorly-written manuscript.

Writing the Rebuttal Letter

The rebuttal letter explains exactly what the authors changed to improve the paper according to the reviewers' comments. Occasionally, reviewers may not fully understand the context of your manuscript.

Regardless, it is important to write your rebuttal in a polite tone. Always state that you appreciate the insightful comments of the reviewers and that their input helped you improve your manuscript and now it is more relevant in your field of study.

Publishing Case Reports

Case reports are relatively easy and quick to write; however, they are notoriously difficult to publish. The reason for this is simple: most medical journals do not publish case reports. Therefore, in order to be accepted for publishing, the case report must be truly exceptional and novel. We encourage scientists to first find a respected journal that publishes case reports on a given topic. We warn scientists to avoid the numerous predatory journals which advertise that they publish case reports just to make a profit (by charging the authors article processing fees). Such journals can be identified by referencing one of the publicly available online lists of predatory journals.

Conducting Research as a Student

As a student without a laboratory, research funding or any patients of one's own, it might seem rather impossible to conduct independent research. Fortunately, there are several options:

1. Systematic reviews (with or without a meta-analysis) are an excellent way of gaining fairly high-impact publications without having one's own laboratory [7]. In fact, the most referenced studies on a given topic are usually provided by systematic reviews and not original papers [8]. Through the writing process, one may learn how to gather, manage and interpret other scientist's findings. The process allows a scientist to conduct an in-depth analysis of previous studies on a particular topic which may help them find something of significance that has not been yet researched.
2. Papers on infodemiology (the epidemiology of information) may be done without a laboratory. One may analyze online health patterns for a particular disease and then relate it to the epidemiology of the disease in a population. Studies such as this may illuminate the overall health seeking behavior in a population [9-11]. Freely accessible databases provided by the World Health Organization, the Centre for Disease Control and Prevention and a country's own health registries are invaluable in these types of papers. Furthermore, with the era of the internet, students can conduct content, readability and quality analyses of popular web platforms (i.e. YouTube, Wikipedia, and Google search results) for a particular disease or topic so that scientists are aware of the quality of information that the public is reading.
3. Letters to the Editor may be written on a recently published article (usually within one month). These letters serve or to augment the understanding of an article or to simply criticize the study. For example, one may write a letter pointing out the significant limitations of a study that were not pointed out in the actual article [12]. One may also analyze the parts of the paper differently [13-15].
4. Several highly respected journals (e.g. JAMA, JAMA Oncology, Annals of Internal Medicine and Journal of Clinical Oncology) feature a humanities column where poetry, personal vignettes and essays may be published on the medical experience [16-18]. These articles often comment on the dynamics of the patient-physician relationship and may offer a social critique of the medical system.

Conclusion

Writing and publishing a scientific article is an ongoing process requiring several revisions and often months of dedication. Although the process can be challenging, we believe it is an incredibly gratifying experience especially with the help of co-authors who share the same passion for medicine. We hope that this guide will be of use to students, residents, fellows, and young faculty members.

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