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Overload of Medical Documentation: A Disincentive for Healthcare Professionals

Jacek Lorkowski, Izabella Maciejowska-Wilcock, and Mieczyslaw Pokorski

Abstract

This review addresses the theories concerning the development and functioning of medical bureaucracy creating an excess of the patient records. An ever-growing number of medical files comply with the typical development of the bureaucratic management of an entrepreneurial organization, an essential feature of which is the life cycle of documentation. When the life cycle ends, an update is created with a multiplication of forms and items to be filled out, resembling that of what happens with the outdated computer program. Yet medical records should have a logical and well-functioning structure using the language of computer science in the form of a cascade or evolutionary model. Further, we believe that mass computerization, in contradistinction to the primary predestination purpose, increases the number of time-consuming medical records, with the evidence that it enhances the occupational burnout among physicians. Clear and concise medical documentation is necessary to handle economic and legal issues in medicine. However, the creation of medical records sits at the crux between a health-conscious provision of the best evidence-driven treatment and the continuum of care and a potential health detriment caused by taking away the time and care devoted to the patient by healthcare professionals. We submit that the hitherto pattern of creating medical records requires a turnabout to attain the intended reasons and user-friendliness for practical ends.

Keywords

Administrative issues · Bureaucracy · Burnout syndrome · Documentation life cycle · Mass computerization · Medical records

1 Background

Almost everything has been said and written about overgrowth and the ever-growing administration in the modern world. Bureaucracy (French *bureau*, office, and Greek *kratos*, power) is a term used since the eighteenth century to describe the sociopolitical and economic reality then prevailing in Europe. The emergence of this concept, in the mid-eighteenth century before the Great French Revolution, was one of the signals

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of impending attempts to change the sociopolitical system, characterized, inter alia, by excessive but inefficient administration (Rothbard 2010). To contend with ubiquitous bureaucracy, Vincent de Gournay (2020) has made a famous line, particularly in the economic field, saying "Let it go, let it pass". This expressive and simple call has become the basis of liberalism. Unfortunately, the State, with its highly bureaucratic formal structures, was an obstacle to the economic freedom at the time.

2 Multifaceted Views on Bureaucracy

Bureaucracy may be defined as the centralized organizational system in which the office mirrors the power (Kłosowska 1998). A more complex, multidimensional understanding of bureaucracy covers all those who deal with administration in a broad sense. Considering not emotional or ecstatic definition, we understand bureaucracy as the people who administer, manage, and organize the work of institutions. The term may, however, be pejorative when it is understood as alienated "power detached from the masses, imposing socially harmful decisions on them" (Kopaliński 1978), which, for instance, was the case during the Great French Revolution. Such a definition is close to the concept of eminent Austrian economist Ludwig von Mises. He believed that the terms "bureaucrat", "bureaucratic", and "bureaucracy" are invectives that have a derogatory connotation (von Mises 2005). That is in strong contrast to the idealistic approach to bureaucracy expressed by Max Weber, who admired the organization system of a fully hierarchical structure. In this model, low-level offices are assigned tasks appropriate to their competences and are then accountable to high-level bureaucrats (Giddens 2004). Max Weber believed that the impersonal relations between officials, in which they exchange information unemotionally through the transmission of documents, are exemplary. Further, a key role in the organization's functioning is played by documentation of its activities. This belief failed to consider the slightest suspicion of a possibility of pathologic relations between officials, including their dehumanization (Kłosowska 1998). Putting the problem bluntly, is it not a description of a specific sociopolitical-economic "perpetuum mobile" Max Weber's conviction that the essence of bureaucracy lies in its enforcing the maximum rationalized behavior means that he failed to consider that bureaucracy often creates an impassable barrier to all innovations and every non-standard way of thinking. That may lead to the paradoxical reversal of bureaucracy's role when administration attaches too much importance to its existence and functioning at the expense of the original subordinate role concerning the social expectations (du Gay 2009). Max Weber and his apologists have failed to consider that the very term administration derives from the Latin word *administrare* which translates as being helpful, servicing, or reaching deeper into the root source, than the term minister which means to serve, implicitly to serve individuals, society, and the State (Szmulik et al. 2007).

Successive generations of sociologists have started to assess bureaucracy much more critically. Robert K. Merton believed that the rigid compliance of bureaucrats with the rules leads to an absurd, unjustified ritual given to his work, or bringing out insignificant details, which brings about negative routine and pathologic emotions toward others. The bureaucrat becomes gradually alienated from his surroundings, feeling like an official, i.e., the man of an institution. The mixing of goals and means creates a specific, bureaucratic vicious circle of thoughts, decisions, and tasks implemented (Merton 2002).

3 Twentieth-Century Perception of Bureaucracy: Parkinson and Peter's Theories

An interest in the issue of bureaucracy has increased in the twentieth century. Cyril N. Parkinson has noticed a steady increase in the number of officials regardless of the actual usefulness of the work they perform. That translates into a social feeling of an excess of officials in the

hierarchical structures of many organizations, i.e., excessive administration. The subject of Laurence J. Peter's interest, on the other side, has been the issue of various white-collar competences and all possible career paths of a bureaucrat, i.e., a kind of "transition from competence to incompetence". He observed that hierarchical officials steadily rise to the level of incompetence, circulating from one post to another as they get promoted, and skills attained while at one post are rarely useful at a successive post, making them incompetent. That way, the terms Parkinson's law and Peter's principle have been coined (Peter and Hull 1994; Parkinson 1957).

Unfortunately, however, according to modern knowledge, neither market economy nor democracy cannot exist without bureaucracy. L. von Mises in the publication *Bureaucracy* has attempted to consider the *sine ira et studio* (without aversion or sympathy) what is hidden under this concept. He pragmatically assumed that the only thing that counts in business is success. Consequently, "the profit motive that guides entrepreneurs to serve consumers according to their best abilities is also the first principle of the internal organization of each commercial or industrial team". The profit also has a direct influence on employees' wages. The employees are free to make independent decisions in the unrestrained capitalist system. Therefore, according to the contract with the employer, they own him a certain amount of work of a specific quality, but nothing more. In turn, the employer expects nothing more than the level of employees' efficiency that deserves the money paid (Bađun 2005; von Mises 2005). A rhetorical question arises of what "specific quality" does mean?

The rational approach outlined above cannot be implemented in all areas of capitalist reality. An entrepreneur or state expects something different from a producer of material goods than from a doctor or nurse "selling their work" in universally understood health services functioning in the free market economy. Additionally, the issue arises of combining Mises' theories with the universal *primum non nocere* concerning medical professionals. If the state has responsibility for the universally understood social protection, which includes healthcare, then it should give up the profit-oriented approach and choose bureaucratic management whenever necessary to fulfill the obligations. These two types of management were distinguished by L. von Mises long before the emergence of a concept of social responsibility of the State (von Mises 2005). Bureaucratic management determines its compliance with the law and budget. The pool of money used in healthcare is set in the state budget, which, in a democratic state, is adopted by parliament or the representatives of a nation (Şimandan 2009). The size of funds depends on the size of a growth domestic product, but also the political will of the parliamentary majority.

4 Bureaucracy and Healthcare

Managers of the healthcare budget must strictly comply with it, in return giving the entire society the most expected health services of the highest standard. This idealistic aspiration remains rather a utopian dream. The implementation of the task is supervised by the bureaucratic health protection system created by the state. At the very bottom of the bureaucratic ladder created for settling expenses are medical staff, i.e., the people who practice the profession of social trust, who are forced to adapt to the barriers resulting from the bureaucratic management. Bureaucracy and healthcare are the terms that form a linguistic antithesis. In practice, it is paramount to balance the contradictions that are inherent in these concepts so that the bureaucratic procedures expected of medical staff would not dominate their work and would not deprive it of the primary role, which is the efficient and effective care over the sick. For the healthcare system to properly function, bureaucracy cannot become the quintessence of negative associations, as von Mises has stated "you cannot measure a doctor according to the time it takes to examine one case" (Peacock 2007). The adopted structure and principles of bureaucratic management cannot become an invariable rigid system, which is referred to as bureaucratism. Bureaucratization is always ossified because it is all about the adherence to

established rules and practices and ossification ultimately turns into petrification and death (von Mises 2005).

5 Threats Resulting from Excessive Bureaucratic Procedures

Public healthcare, whose functioning cannot be all profit-oriented, is financed from the state budget. Bureaucratic expectations, which to an extent are necessary, should strengthen its functioning rather than paralyze it through an excessive amount of documentation, to reduce the impact of stressors on the medical staff. When medical staff is overstressed, the possibility of professional miscalculation increases but also triggers emotions that are not indifferent to the patient and his assessment of the therapy process. A theory of instant cognition of Gladwell, called "thinning into slices", states we all have an unconscious ability to see patterns in a variety of situations and behaviors (Gladwell 2005). This ability is based on personal experience and observations that are self-registered by the brain in a noticeably short time. When we converse with somebody, we can instantly assess the person. From a psychological standpoint, it is like a flash in the brain. Particularly, the ending element of the matter analyzed is of special importance. This theory came from the elaboration that was based on filmed conversations and interactions of couples who were trying to avoid a threatening breakdown of a relationship. Verbal and nonverbal conversations mainly affected emotional memory. A mathematical computer-driven analysis of video recordings split into several second bins (thin slices) showed that the biggest threat to the relationship was a disdain exhibited by one or both sides and an attempt to push the partner to a lower level (Eichenbaum 2017; Voss et al. 2017; Carrère and Gottman 1999). Contrary to what it could appear, the theory is universal and may be directly transposed to the issue of bureaucracy, including bureaucratization of healthcare system functioning. The state, i.e., bureaucratic administrator, expects the optimal use of the allocated budget and the implementation of all procedures required, with the appropriate number of documentations. The society, i.e., patients, is interested in treatment and its effects. The disproportion in the public health service that is growing between the time needed for the administrative purpose and that needed for the patient care is increasingly unfavorable and traumatogenic for the patient in contact with the system and the physician, leading to stress and tension (Brongel and Lorkowski 2007). A dissatisfied patient/client expresses his indignation and/or asserts his rights in the court. It turns out that when patients question the way they are treated, they often accuse the doctor of mistreating him. The patient's subjective feeling is dominated by the amount of time devoted to them, kindness, calmness, and readiness of the doctor to listen and explain often illusory problems. These elements, which constitute the essence of empathy, often affect the subjective assessment of the entire therapy. This is how the problem as seen by lawyers taking part in legal proceedings brought up by dissatisfied patients (Allen and Burkin 2000; Levinson et al. 1997). Ambady et al. (2002) has attempted to rationalize the patients' allegations, based on Gottman's theory of thin slices (Goldman et al. 1996). She analyzed the intonation, timbre, and rhythm of surgeons' statements during their conversations with patients. The results were akin to those obtained by Gottman in his study devoted to couples trying to save their marriages. Irrespective of the doctor's qualifications, such nonmedical factors have a significant influence on claims of the dissatisfied. Likely, the stressed physician's "racing against time" and excessive bureaucratic duties belong to this group.

The question arises of whether anyone has ever calculated the costs of not spending time on the patient and devoting it instead of creating excessive medical records. Has it been calculated what the costs look like, in both money and time, of the elaboration of ever more extensive, obligatory medical documentation by a surgeon before completing an operation? Our literature search failed to provide any evidence of research to this end. Potential indirect costs (lost opportunity costs) are high. Our provisional estimation,

based on the causal relationship possibly present in such a case, involves a combination of (1) fatigue, i.e., not optimal surgeon's psychophysical form; (2) primary outcome, i.e., imperfect surgery; and (3) secondary outcome, i.e., longer patient's recovery, convalescence, and possible complication, all of which extends the time spent on sick leave, with obvious personal and societal costs.

6 The Necessity to Limit the Load of Medical Documentation

Data appearing in the patient's documentation, theoretically, are required for making the accurate diagnosis and optimally to treat the patient. Often, however, excess data does not facilitate but hinders diagnosis. That may be exemplified by a case in the Cook County Hospital in Chicago at the end of the twentieth century, where the number of patients reporting chest pain suggestive of heart infarct was so large that it threatened the collapse of hospital functioning. Brendan M. Reilly (Reilly et al. 2002a, b), head of the Hospital Medical Institute, has rationalized the way of admission to the intensive care unit by using a diagram algorithm developed by Goldman et al. (1996), consisting of four basic cardiovascular symptoms which would suggest the need for imminent hospitalization. Each doctor was obliged to follow the decision-making algorithm. The system introduced rescued the hospital's logistical and financial situation with no harm done to the patients. This example was shortly followed by other medical institutions. This example shows that too much information accumulated for the best patients' benefit could have an unintended effect, introducing information noise. Medical staff, especially in urgent situations, with limited time at disposal, is not capable of the evaluation of an excessive amount of data. No essential supporting data becomes meaningless in a life-threatening condition. Interestingly, it has been a quarter of a century since the effort to control the catastrophic situation in the Cook County Hospital, but the Goldman algorithm still works in cardiology. The practice has shown that fewer documents and data in the doctors' hands often work better than more documents for making the right decision. Unfortunately, this is not always the rule. At present, the situation may somehow change due to computer use. However, without the introduction of artificial intelligence systems, the amount of information that can be logically processed by the man in a limited time is not unlimited. When a new document is needed to complete a previous document, one starts to mull "is it not one document too far", decreasing the potentially positive intention of the previous document. Has bureaucracy not exceeded the red line of becoming detrimental to the quality of treatment? Rapid multidisciplinary development of knowledge related to human health generates an increasing amount of documentation so that the process of bureaucratic management is continued, which is amplified by the administrative structure of healthcare. Medical staff is involved in the process, regardless of individual objectives or subjective assessments.

Actions for the benefit of someone else's health had already been known at a time when there was not yet an extensive bureaucratic structure in place. Most of the rational activities of *Homo sapiens* followed the principles as follows: (1) I act according to the scheme "a". (2) I just came up with an idea that the scheme "b" is better. (3) Therefore, I substituted the scheme "b" for scheme "a" if the scheme "b" works. In the case of medical records, another mechanism works. In a simplified way, it can be presented as follows: (1) I have and fill in the document "a". (2) I came up with the document "a + 1". (3) I will fill in both document "a" and "a + 1". A rhetorical question remains whether that applies to infinity in the face of the mathematical principles introduced by Francesco Maurolico in the *Arithmeticorum Libri Duo* of 1575.

7 Functioning Models of Medical Documentation

An analysis of the problem of the growing avalanche of documentation cannot be complete

without considering the emergence of new technologies in the universally understood information technology (IT) industry. Currently, mainly in the United States, medical records should be generated as e-records. Discussing this issue in detail goes beyond the scope of this article. However, it seems necessary to consider the most important common elements of the standard and electronic documentation (Evans 2016; Kruse et al. 2016). When reviewing the literature on the subject, attention should be given to the outstanding work of a British anthropologist, Matt Spencer, at the Faculty of Physics of the Imperial College London (Spencer 2015). He investigated fluid dynamics, but the results of his research are universal and can be transposed to the creation of computer programs as well as multifaceted human activities. The software he originally used was complex and well developed. However, the emergence of new research topics and tasks to be interim resolved required the addition of further functions to the software. Over time, the program expanded to over a million lines of code in many different computer languages. Over time, the horrendous amount of software overwrites has made it increasingly complex and susceptible to failures or unforeseen errors in calculations. That eventually decreased research productivity. Fewer results obtained led to a reduction in the number of publications and patent implementations and consequently decreased individual track records and the faculty level. That, in turn, caused permanent stress for the employees using the software, followed by a gradual psycho-mental downward trend of the entire research teams, expressed as frustration, apathy, and discouragement.

Spencer's research should be considered in the elaboration of algorithms for creating medical records, including handwritten ones. Based on the regularities he has described, we might expect a problem of not duplication but the multiplication of the same documents. People have a different threshold, beyond which the generation of subsequent elements of documentation causes only frustration and then the quality of work, including the very documentation, rapidly declines (Spencer 2015). The question is not if but where lies this point beyond which making the manifold of medical records should be terminated for the good of medical staff and patients, even though the overseer of the bureaucratic procedure may feel increasingly good.

In 1975, when the development of the entire IT industry was still far from today's, Frederick Brooks, an IBM engineer, published an iconic novel in computer science entitled *The Mythical Man-Month* (Brooks Jr 1975). He has described the life phases of the computer program, which largely reflect the economic life phases of an enterprise. In the growth model of Greiner, the following phases are distinguished: entrepreneurial, cooperation or collectivity, centralization and control, and innovation or decentralization (Greiner 1994). Each may be preceded by a specific crisis such as a leadership crisis, an autonomy crisis, or a control crisis. Formalization, a key feature of the control phase, has to do with the growing bureaucracy, hence the nickname "briefcase phase". This is the phase when employees stop understanding the system and often rebel against it. Finally, the last stage might be the crisis of renewal which usually is spurred by too much of opening out and flattening of the organization.

In the case of a computer program, the idea appears first, and the requirements for the planned software are determined. Then, the software design appears, followed by its implementation, testing including validation and verification, and finally the program use and maintenance, provided that the program remained unchanged. This example outlined above applies to the cascade model in which each next phase begins after the preceding one. The evolutionary model is more complex as the strict linear sequence of phases is given up. In turn, the component model is simpler as ready-tested modules of other software are used (Lau and Wang 2007).

The life cycle of a computer program may suddenly end up in crisis, as may the life cycle of an organization. A well-promising and well-performing computer program may get expanded to a larger program. Most often, it is a component extension that increases the number of codes. The reason may be the update of old embedded codes with modern extensions or adaptations matching

the current personal needs. The program works and its developmental cycle continues. At some point, however, the users' expectations become higher and remain unmet and unsatisfied. When the critical mass of mismatch is reached, the program, once an optimal tool, becomes archaic and thus deserted. This process has been called "tar pit" (Brooks Jr 1975).

The question arises if the Greiner model of a computer program's life cycle can be applied to medical records. Let us look at the entrepreneurial phase of the model. It discusses the creativity and innovation of the entrepreneur. Is the enthusiastic doctor, writing down all relevant notes about the patients he treats, or a diligent student, making notes on the most important symptoms he finds in the patients examined, an equivalent of this phase? A lot of information must be gathered, but an excess information noise is only counterproductive. The second phase of the model is collectivity in which the emphasis is put on the identification of the right goals and procedures. Referring to the doctor, the patients he treats, and the medical documentation he creates, this is a moment when the first decision-making automatism in treatment and the first patterns of entering notes in the documentation appear. The third phase of the model is centralization and formalization where patterns, rules, and policies concerning the doctor's activities are made, resisting the attempts to "delegation" of medical and managerial responsibilities to other persons. In the doctor's analogy, he would take care of all patients himself, using "paste in" patterns of descriptions in the documentation. This phase is fraught with errors in medical records found by auditors, which are not only formal oversights but ignorant or delinquent deviation from truth or accuracy in documenting diagnosis and treatment, which may result in an unsatisfactory outcome. Notably, the largest number of irregularities is usually recorded in the outpatient documentation (Greiner 1994). Finally, the last phase of the model is decentralization of diversification of responsibilities, often combined with organizational innovations. Thus, the doctor would not treat all patients himself, but refer them to other staff, specialized in the same or other fields. From a logistic standpoint, diversification would concern both treatment and creation of medical records.

Analyzing the problem in Poland, the auditors have noticed that the results of the latest audit regarding the status of medical records are confusingly akin to the audit from 10 years back. That may highlight a low awareness of the importance of documentation for the correct treatment process among medical staff who regard the completion of documentation as a bureaucratic obligation, taking too much time (Report 2020). That seems to be a chronic situation then and now. However, the assessment of the cause of the problem may be different than stated above. First, one should consider whether the scores of employees do not take their duties seriously and underestimate them for no reason. Perhaps, for a task which takes "n" minutes to complete, medical staff can devote only half or less of the time required, or else they must forgo some other obligations. The use of auxiliary staff pointed out by the auditors does not resolve the issue and is rather secondary. It seems more important to focus on the implementation of new IT technologies and to use them for the good of documentation completion.

The evaluation of the phase of a "briefcase crisis" raises the question of what's next. According to the Greiner model of the life cycle of the organization (Greiner 1994), if the patient's diagnosis is correct, the cooperation phase should begin to appear as a response to the current crisis, decentralization, breaking routine, reorganization, and a participatory management style. Comparing the life cycle of medical records to that of a computer program, the cascade model, which is long since used, seems slightly better than the Greiner model. The cascade model consists of the specification of requirements, system design, implementations, testing, and use. Other possibilities are the evolutionary and component models. New innovative, necessary, and improving treatment quality components of documentation are steadily overlaid in the evolutionary and component models. All that is intertwined but no continuity of the rules is indispensable. In the case of entrepreneurial organizations or computer

programs, the life cycle inevitably comes to an end at some point in time. A new cycle is set up and begins its life, which is often labeled as the return of common sense and normality (Spencer 2015). Medical records share a similar fate. They must have logical and well-functioning structure, not a series of overlays, using the language of computer science in the form of a combined cascade and evolutionary models. The problem is compounded by the fact that some elements of medical documentation are decades old, while others are just beginning to appear with time. Convincingly, creation of a new pattern of documentation, optimally ubiquitous to be used at the international level, does not seem more difficult than writing new codes for Windows 10 operating programs, where the programmers also must discard previous patterns of software. The appropriate overlays should be created for specific specialties. The system should form a uniform whole, not made up of clusters of documents that do not match each other.

8 Occupational Burnout and Medical Records

The sentence uttered by Spencer (2015) "I just want to do science!" may be transposed into words spoken by doctors from all corners of the world: "We just want to cure people, not be secretaries". Likely, a large proportion of healthcare managers do not necessarily accept that. A series of studies by Maslach (1982, 1998), a psychologist from the University of Berkeley, has been devoted to the phenomenon of burnout in persons associated with universally understood healthcare. The three inseparable components of occupational burnout distinguished are as follows: feeling of emotional exhaustion, depersonalization (cynical, instrumental attitude toward others), and a sense of personal inefficiency. Generally, burnout is a serious and increasing problem in the medical profession (Maslach and Schaufeli 1993). In the United States, burnout syndrome in medical professionals has been sharply on the rise in the twenty-first century, reaching a dimension previously unknown. In 2014, 54% of physicians reported at least one of the three symptoms of burnout, compared to 46% several years back. The cause-effect relationship of this phenomenon involving the introduction of excessive documentation and the current need for its digitalization is evident. Overtime work has been, at least partially, an aftereffect of the growing medical bureaucracy. According to the Mayo Clinic research, occupational burnout increases the likelihood that experienced doctors switch to part-time work, the thing previously little known in the US medical market (Patel et al. 2019; Abdulwahid et al. 2018; Gawande 2018; Maslach and Leiter 2016). A reduction in the optimum use of the key resource of physicians, i.e., their training in taking care of patients, is a new sociological phenomenon in the United States whose distant effects are open to conjecture. It may, however, be assumed that the process will result in socioeconomic losses of many dimensions. The percentage share of the best-educated specialists, predisposed to treat and supervise the treatment of the most difficult disease cases, declines in the medical labor market. Thus, patients become less likely to get the optimum help, and the time to get help gets longer, which adversely affects therapy outcome, work absenteeism, and increases the costs of lost opportunities from the state's perspective.

Occupational burnout appears to vary depending on the medical specialty. It is more frequent and stronger in emergency medicine staff compared to other specialties. It appears that the amount of time spent completing medical records, which takes place electronically these days, plays a role in these differences. Further, it is a strong predictor of burnout. Surgeons spend relatively less time in front of a computer, but emergency doctors do the opposite in this respect. This is called the "effects of being screen-bound" (Abdulwahid et al. 2018; Gawande 2018). The question arises of whether increasing bureaucratic requirements comply with the foundation of medical ethics, i.e., to provide the best impartial and fair-minded healthcare to patients. Another issue that should be noted regarding the vast number of medical records is the atomization of human

teams. Their members become increasingly disconnected, and they rarely communicate with each other, being overtaken by completing the forms. New components of documentation transfer more responsibilities to doctors. Such components, even if justified, further depersonalize and reduce the role of the man. Unfortunately, patients are the fastest-growing group of consumers of electronic medical records. They often get distracted by confusing descriptions, not serving any useful diagnostic or therapeutic purpose, and seek advice or a second opinion not from doctors but rather from the Internet sources. Doctor Google syndrome decreases the ethos of the medical profession and trust in doctors, as well as the efficiency of healthcare services.

Gawande (2018) has posed a basic question concerning the system of generating medical records: "Is it a correct and optimal situation when people using the healthcare system, are more and more satisfied and those who help them, within their professional capacity, more dissatisfied?" To answer this question, the author invokes the old concept of "taylorization". Frederick Winslow Taylor (1856–1915), a representative of the engineering trend in the management of the time, created a concept that to achieve the greatest optimization and intensification of work and the best use of production means the maximum specialization should be used in the form of bestowing an employee with one task only. That would lead to perfectionism, standardization, and rationalization and speed of operations (Turan 2015). Transposing Taylor's concept to medicine, the empirical experience of generations of doctors indicates that 90 percent of patient cases are similar. The United States was the first country to introduce real subspecialties on a massive scale. One doctor performs, for instance, a trace number of different types of treatments but performs each on a large scale and must create necessary binding documentation. The burnout resulting from this type of performing professional medical activity has been described (Gawande 2018). However, some cases go above and beyond the standard. That puts the assumption of "taylorization" in medicine into question.

In conclusion, research clearly shows that the growing load of medical records and documentation, despite mass computerization, leads to an increase in the occupational burnout among physicians. Based on theoretical models, analogous to those used in the evaluation of the "life cycle" of computer programs, it appears that the pattern for creating medical records requires a rewriting into a more restraint if not penurious manner. It does not seem reasonable to demolish the hitherto system without proposing, introducing, and testing a new one. It should be borne in mind that a clue for resolving many issues is to put forward a thesis and antithesis and create a synthesis.

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Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs

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Abstract

Vaccination against pneumococci is one of the most effective methods of preventing pneumococcal diseases. Currently, 10- and 13-valent conjugate vaccines (PCV10 and PCV13) and 23-valent polysaccharide vaccine (PPSV23) are used. Only the conjugate vaccines are used in children. The PCV can be used both in children and adults, but children can receive only PCV. A side effect of vaccination was that bacterial serotypes not included in a vaccine started increasingly emerging in pneumococcal infections, replacing the serotypes eliminated by the vaccine. The basic vaccination schedule consists of three or four doses, according to the country's recommendation. In Poland, it consists of two primary doses followed by a supplementary dose of the PCV-10, with some modifications in case of specific risk factors. The use of preventive vaccinations has helped reduce antibiotic resistance, as serotypes characterized by a rapid acquisition of drug resistance are included in the vaccine serologic spectrum, making their environment prevalence decrease. The research is currently underway on conjugate vaccines that contain a greater number of bacterial serotypes and on more universal vaccines that would eliminate the emergence of new serotypes.

Keywords

Pneumococcal vaccine · *Streptococcus pneumoniae* · Invasive pneumococcal disease · Vaccination program

1 Introduction

Pneumococcal diseases, especially invasive forms of infections, are a common cause of illness and death in patients of all ages. Children under the age of 5 and the elderly 60–65+ are at the greatest risk of developing a severe disease course. To prevent infection, vaccines are used to induce specific immunity against bacteria. The first was a polysaccharide vaccine that contained purified antigens from the bacterial envelope. Currently, the polysaccharide antigens are available in the 23-valent vaccine, PPSV23, that works through mechanisms other than T lymphocytes and, thus, is unable to induce adequate immunity in young children. To induce an effective immune response in children, a combination of bacterial polysaccharide with a carrier protein has been developed, a pneumococcal conjugate vaccine (PCV). This vaccine was initially available in a 7-valent form (Prevenar), in which the CRM197 protein was a carrier, followed by 10-valent (Synflorix) and 13-valent (Prevenar 13) forms in

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which the protein D and CRM197 were used as carriers, respectively. There is also a 10-valent vaccine (Pneumosil) that uses the CRM197 protein, available on the Indian market.

Two pneumococcal vaccines are in use in Poland: Synflorix (PCV10) and Prevenar 13 (PCV13). The first is indicated for the use in children from 6 weeks to 5 years of age, while the other is for children from 6 weeks of age and adults. Currently, 146 countries use the preventive pneumococcal vaccines as part of vaccination programs, with 138 programs being national. As of March 2020, 15 other countries plan to introduce such vaccination. Most developed countries have a schedule of two primary immunizations and a booster dose. The estimation has been that more than 61 million infants have been vaccinated against pneumococci, which is about half infants worldwide (IVAC 2020).

2 Invasive Pneumococcal Disease: Definition and Epidemiology

Streptococcus pneumoniae (*S. pneumoniae*) is a common pathogen in people of all ages. In some instances, it does not cause clinical symptoms, although is present in the upper respiratory tract. In other cases, it is responsible for infections that can be divided categorized as non-invasive (e.g., otitis media, paranasal sinusitis, or pneumonia without bacteremia) and invasive (e.g., meningitis, sepsis, or pneumonia with bacteremia). In the latter case, the contagion and its genetic material are isolated from the physiologically sterile site (EC 2002).

The occurrence of invasive pneumococcal disease (IPD) must be obligatorily reported to provincial sanitary and epidemiologic stations in Poland. In 2018, there were 1,354 IPDs reported in the country, with the incidence of 3.52/100,000, of which only one patient was not hospitalized. Additionally, there is a voluntary case reporting system to the National Reference Center for Bacterial Meningitis (NRCBM), which includes the determination of bacterial serotypes. In this system, laboratory confirmation of IPD was obtained in 1,037 cases, which translates into an average detection rate of 2.70/100,000 in 2018; these figures were 1,088 and 2.83/100,000, respectively in 2019. More than half of the diagnosed cases resulted in death, which translates into a mortality rate of 39.8% (NRCBM 2020; NIPH-NIH 2019; NRCBM 2019). Overall, the incidence of IPD-related meningitis or encephalitis in children of up to 5 years of age and adults 60+ was above the average of all registered cases. The NRCBM recommends the use of a term detectability rather than morbidity because the incidence of IPD is likely underestimated due to the early initiation of antibiotic therapy and scarce blood culturing. For comparison, 24,663 cases of IPD were reported in the European Economic Area in 2018, which gives a detection rate of 6.39/100,000. Data on the mortality rate have been reported by only 18 EU countries, with an average of 15.3%. Like in Poland, children below 5 and adults above 65 years of age were most often affected (ECDC 2020).

3 Historical Vignette on Pneumococcal Vaccination

The first large-scale research into a vaccine to prevent pneumococcal disease began in 1911. It was then that pneumococcal disease decimated miners working in South African gold mines. Wright et al. (1914) used killed bacteria to perform vaccinations and their research group consisted of over 50,000 mine workers. In the short term, there seemed to have been an impression that although vaccinated subjects fell ill, they died less frequently. This difference became indistinguishable about 4 months after vaccination, and detailed analysis showed the vaccine failed to reduce the risk of death in the course of pneumococcal disease. In a later research, Lister (1916), who described eight different serotypes of *S. pneumoniae*, has suggested that the dose of killed bacteria originally administered by Wright was too low. Soon afterward, Dochez and Avery (1917) found that bacteria produce a water-soluble proteinaceous substance that is resistant

to the action of trypsin and induce immunological activity. The next milestone was set 6 years later by Heidelberger and Avery (1923) who showed that this substance was a polysaccharide on the pneumococci capsule. Later on, attempts were made to create an effective vaccine, but the first significant effects were achieved no sooner than in the 1970s. Smit et al. (1977) investigated the effectiveness of 6-valent and 12-valent polysaccharide vaccines among gold miners in South Africa. The results were remarkably good as the vaccines were well tolerated and reduced the risk of pneumococcal pneumonia by 76% and 92%, respectively. Those findings contributed to the approval of the first pneumococcal vaccine in the USA in 1977, consisting of 14 serotypes, which was increased to 23 serotypes in 1983.

The empirical experience has been that children are much more vulnerable to pneumococcal infections than are adults. The reason is that the immune system of children weakly responds to bacterial polysaccharides administered in the vaccine (Davies 1937). The cause of this phenomenon was brought to light by Stein (1992) who showed that the polysaccharides of bacterial envelope belong to thymus-independent antigens; the immune response develops at a later age as also does the immune memory that upholds the effect of vaccination. A resolution to this issue became a combining of a carrier protein to the bacterial polysaccharide. Although successful research on the issue had already been performed in animal models in the 1930s (Avery and Goebel 1931), it took decades more to replicate that in a safe way for humans, developing the most advantageous polysaccharide-protein combination. The effectiveness of the conjugate vaccine has been verified toward the end of the twentieth century in the youngest children (Ahman et al. 1998), followed by a registration of the first pneumococcal conjugate vaccine (PCV) in 2000. It contained polysaccharides of seven bacterial serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) combined with a diphtheria toxin protein variant (CRM197). This protein did not cause disease symptoms but significantly increased the response of the immune system to polysaccharide antigens linked to it. The PCV vaccine has been repeatedly improved since, by adding more serotypes and modifying the carrier proteins and finally by changing the carrier protein for a single serotype only. Multicenter studies have shown that a 10-valent vaccine based on a combination of most polysaccharides with a protein D of non-enveloped *Haemophilus influenzae* strains is as effective and safe as a 7-valent vaccine used before but covers a wider spectrum of pneumococci (Bermal et al. 2009; Vesikari et al. 2009). A 10-valent vaccine containing conjugated polysaccharides of the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F got final approval in 2010.

Concurrently, research was underway to further expand the number of serotypes available in a 7-valent vaccine while maintaining a modified diphtheria toxin as a carrier protein. Conjugated polysaccharides of serotypes 1, 3, 5, 6A, 7F, and 19A were added to the previously known 7-valent vaccine, resulting in a vaccine covering 13 serotypes of *S. pneumoniae*. The new vaccine appeared equally effective and safe as its predecessor and has protected against the serotypes whose occurrence increased in the environment due to the use of a 7-valent vaccine in previous years (Bryant et al. 2010; Kieninger et al. 2010; Dinleyici and Yargic 2009). Ultimately, the 13-valent vaccine was approved in 2010, replacing the 7-valent vaccine. New conjugate vaccines that protect against more serotypes using novel mechanisms to induce immune response are currently under development. The future epidemiologic situation will likely depend on the effects of new vaccines as the serotypes present in the current vaccines are going to be reduced or eliminated from the environment.

4 Influence of Vaccination on Epidemiology of Pneumococcal Diseases

In 2000, it was estimated that 826,000 children younger than 5 years died from pneumococcal diseases, which accounted for 11% of all deaths (O'Brien et al. 2009). Eight years later, after the introduction of vaccination against pneumococci,

the number of deaths decreases to 541,000 or 6% of all deaths in this age group. Most fatalities occurred in Asia and Africa, although they also occurred in Europe and North America (WHO 2008). The death rate has kept on decreasing in further years. In 2015, there were 317,300 children in this age group who died from pneumococcal diseases. Wahl et al. (2018) estimated that the conjugate vaccine prevented the death of approximately 250,000 children between 2010 and 2015. Mass use of pneumococcal vaccination is believed to be a primary cause of death reduction.

A 7-valent vaccine was originally approved in the USA and its introduction resulted in decreased IPD incidence from 24.3/100,000 in 1998/99 to 17.3/100,000 in 2001. The decrease was most notable in children less than 2 years of age where it was from 188/100,000 to 59/100,000. Importantly, vaccination reduced the incidence of penicillin-resistant pneumococcal infections by 35% (Whitney et al. 2003). Similar effects were noticed in Europe where the IPD incidence in children was 44.4/100,000 with an average mortality of 3.5% before PCV7 introduction and decreased to 32.5–23.4/100,000, depending on a country, after PCV7 introduction (Isaacman et al. 2009). A systematic review of studies examining the worldwide prevalence of pneumococcal serotypes causing IPD has shown that seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) account for more than half of all IPD cases, with the serotype 14 being the most common among them (Johnson et al. 2010). Serotypes included in PCV7 cover 71% of bacteria, while PCV10 and PCV13 cover 7% and 16% more, respectively (Isaacman et al. 2009).

5 Optimal Vaccination Schedule

As recommended by the WHO, pneumococcal vaccination using conjugate vaccines can be performed either on the 3 + 0 schedule, starting at 2 months of age, with a minimum interval between doses of 4 weeks, or on a 2 + 1 schedule with an 8-week interval between the primary doses followed a booster dose between 9 and 18 months of age. The timing for a booster dose is, however, rather poorly defined. An additional booster dose should be given to HIV-infected or premature babies (WHO 2019a). Pneumococcal vaccination should be combined with diphtheria, tetanus, and pertussis vaccines or any other vaccine containing components thereof (WHO 2019b). Studies show that the 2 + 1 schedule increases the antibody content more than the 3 + 0 schedule, but both provide a satisfactory increase over the protective level. The only exception is the serotype 6B for which the 2 + 1 schedule provides a significantly better immune response (IVAC 2017; Conklin et al. 2011).

Initially, studies on the conjugate vaccine guided by manufacturers pointed to the effectiveness of a 3 + 1 schedule that was registered for the general use. Later, a 2 + 1 schedule has been accepted as a possible alternative, particularly when the vaccine is given as part of a vaccination program. Givon-Lavi et al. (2010) compared the 3 + 1, 3 + 0, and 2 + 1 schedules and showed that the reduced 2 + 1 schedule resulted in lower levels of postprimary IgG content in children when compared to the 3 + 1 and 3 + 0 schedules for serotypes 6B, 18C, 19F, and 23F. Although both 3 + 1 and 2 + 1 had pronounced booster responses in the second year, the latter responded less. The 3 + 0 schedule resulted in the lowest levels of IgG responses in the second year. In another study, a comparison of two-primary with three-primary doses shows that both schedules induce a strong immune response, with the three-dose schedule yielding higher protective antibody titers, especially for serotypes 6B and 23F (Scott et al. 2011).

A concentration of protective antibodies is a good and easy method of determining the vaccine immunogenicity, but it is impossible to directly translate that to the clinical protection of a patient. Dagan et al. (2012) investigated how a given vaccination schedule affects the carriage of *S. pneumoniae* in the upper respiratory tract. A three-prime dose schedule was found to better prevent against carrying the serotypes against which the vaccine protects compared to a two-prime dose schedule, but the difference disappeared with a booster dose, and giving two booster doses further reduced this risk of infection.

A booster dose immunization schedule is used in most developed countries, except Australia where the 3 + 0 schedule was in place used between 2005 and 2018. At that time, the effectiveness of PCV7 and its replacement, PCV13, in 2011 in preventing IPD was investigated. While there was a small, stable number of IPDs caused by vaccine serotypes in case of PCV7, their number caused by serotypes included in PCV13 gradually increased. Serotype 19A was the leading cause of IPD in Australian children despite being contained in PCV13. Studies indicate that the vaccine is effective but the protection it offers wears off over time, especially within 2 years after the last dose. Thus, it is essential to give a booster dose. Since it is given to an older child, it elicits a stronger immune response and protects during the time of a greater hazard of invasive infection. In effect, the Australian government has changed the vaccination schedule from 3 + 0 to 2 + 1 as of September 2017 (Australian Government 2020; Jayasinghe et al. 2018).

6 Preventive Vaccinations in Poland

In Poland, vaccination against pneumococci became available free of charge only to children at risk as of 2008. The situation has changed in 2017 when mass vaccination against pneumococci for children born after 31 December 2016 was introduced into the Preventive Vaccination Program. In most cases, the 2 + 1 schedule is used, i.e., two doses of primary vaccination 8 weeks apart and one dose at least 6 months after the last primary dose. The 3 + 1 schedule is reserved for children at risk due to epidemiologic or clinical reasons and children born before the 37th week of pregnancy or with a birth weight < 2,500 g. The PCV10 is primarily used, except for children from risk groups or those born before the 27th week of pregnancy when the PCV13 is preferable. A child qualifying for a free PCV10 may be immunized with PCV13 at the guardian's expense.

Before introducing pneumococcal immunization for all children at the country level, some municipalities implemented local preventive programs to reduce IPD and other pneumococcal diseases. An example of the greatest success is the city of Kielce, inhabited by about 200,000 people. In 2006, free PCV7 immunization was introduced there for all children under 2 years of age in a 2 + 1 schedule. After 5 years, PCV7 was changed to PCV13. The program proved successful, vaccination coverage was almost 100%, and the number of deaths due to pneumococcal pneumonia in children <2 years of age decreased by 82.9%, and it also decreased in adults >65 years of age by 43.5%. Apart from confirming that pneumococcal vaccination reduces the incidence of IPDs in children, this program has shown that the issue of herd immunity is not insignificant, as the immunization of children also protects the elderly from the disease (Patrzałek et al. 2016). It is possible that indirect immunity to the elderly, achieved by mass immunization of children, is more effective than direct immunization of children. A postulated explanation of this phenomenon is a weaker immune response in the elderly (Patrzałek et al. 2012; Simonsen et al. 2011). The percentage of 2-year-old children vaccinated against pneumococci in Poland was 94.1% in 2018 (NIPH-NIH 2019). A primary goal of mass vaccination is to reduce the incidence of IPDs. However, vaccination also protects against other pneumococcal diseases, which raises prospects of a reduction in pneumococcal pneumonia or acute otitis media (Gajewska et al. 2020; Górska-Kot et al. 2019). A detailed evaluation of the epidemiologic effects on the general population of mass pneumococcal vaccination in children requires a much longer time than the 4 years elapsing now from its launch in Poland.

7 Vaccinations and Distribution of Serotypes

In Belgium, PCV7 was introduced into the immunization program in 2007. The number of IPD cases was since then steadily decreasing. The PCV7 was switched to the PCV13 in 2011, with a further reduction in IPDs. In 2015/16, the PCV13 was switched to a 10-valent version, as both vaccines were considered equally effective. However, just 2 years after this switch, the

number of IPDs began to increase, due mainly to serotype 19A whose appearance increased tenfold (Desmet et al. 2018). The increasing use of pneumococcal vaccines has changed the distribution of pneumococcal serotypes. Initially, between 2000 and 2008, most serotypes causing IPD were contained in PCV7. Due to active and specific immunity-induced against vaccine serotypes, they were later replaced by serotypes originally absent in vaccines. For comparison, in 2015, PCV10 covered serotypes accounting for 53.6% of IPD in children <5 years of age in Poland and PCV13–75.0%, while in 2019 these percentages dropped to 30.2% and 45.3%, respectively (NRCBM 2020).

After the introduction of PCV7 into the general vaccination program in Europe, a reduction in IPDs caused by the vaccine serotypes was noticed, with an increase in the appearance of other serotypes such as 1, 3, 7F, and 19A. Where the PCV13 was used, the incidence of IPD caused by serotypes 1, 6A, 7F, and 19A decreased, and where PCV10 was used, the incidence caused by serotypes 3 and 19A increased (Htar et al. 2015; Weil-Olivier et al. 2012). The 2019 epidemiologic Polish data show that the IPD-related deaths are mainly caused by serotypes 3, 4, and 19A (NRCBM 2020). Since, akin to other European countries, Poland uses the PCV10, a higher IPD mortality rate could be expected due to an increase in serotypes 3 and 19A, with lower mortality due to other serotypes contained in PCV10. A biologically plausible explanation of why only two out of three PCV13 serotypes absent in PCV10 (3, 6A, and 19A) infect a significant number of people can be found in a long-term study of PCV10 effects on IPD in Finland. That study shows that PCV10-vaccinated children not only produce immunity directly to the vaccine antigens but also cross-reactive immunity to serotype 6A that is absent in this vaccine (Rinta-Kokko et al. 2018).

8 Antibiotic Resistance

The introduction of mass vaccination against pneumococci has made it possible to reduce the number of strains resistant to antibiotics, but the problem of antibiotic resistance is still present. Mass vaccination with PCV7 increased the incidence of IPD caused by serotype 19A that aside from being a common cause of IPD also is characterized by frequent antibiotic resistance (Isturiz et al. 2017; Dagan and Klugman 2008). Serotypes most frequently resistant to a spectrum of antibiotics in Poland in 2019 were 6B, 6C, 6D, 14, 19A, and 19F. The use of PCV13 could ultimately prevent 83%, 100%, and 77% of infections caused by strains resistant to penicillin, third-generation cephalosporins, and erythromycin, respectively, and as many as 89% of infections caused by multi-drug-resistant strains (NRCBM 2020). This underlines the importance of vaccination in reducing the problem of antibiotic resistance, particularly when the number of resistant bacteria is constantly increasing.

9 Future of Pneumococcal Vaccination

Conjugate vaccines are currently in a research phase, covering more serotypes of bacteria. A 15-valent vaccine containing two serotypes (22F and 33F) more than a 13-valent vaccine shows satisfactory immunogenicity and safety (Stacey et al. 2019). A 20-valent variant containing additional serotypes 8, 10A, 11A, 12F, and 15B has successfully passed initial clinical trials (Thompson et al. 2019). The number of pneumococcal serotypes is quite large, so it has been decided to search for alternate ways of vaccine development other than adding on serotypes. Whole-cell vaccines prepared from selected strains of *S. pneumoniae* with reduced virulence seem a promising breakthrough in vaccination against pneumococci. Such vaccines would result in the production of antibodies directed at different pneumococcal antigens regardless of their serotypes and obviate the need to purify individual polysaccharides, sparring vaccine costs. Initial clinical trials are quite promising, and a whole-cell vaccine may shortly join the range of pneumococcal vaccines (Morais et al. 2019).

The most appropriate direction in the development of pneumococcal vaccination seems a search of a vaccine that protects against the

bacterium, regardless of its serotype. This idea is supported by the constantly changeable distribution of serotypes toward other than those present in the spectrum of hitherto available vaccines. Given a large number of pneumococcal serotypes, it would be very difficult to develop a polysaccharide or conjugate vaccine protecting each serotype. Finding a universal pneumococcal target for the vaccine seems the only reasonable way out of this predicament.

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Serum Vitamin D and Immunogenicity of Influenza Vaccination in the Elderly

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Abstract

Vaccination is the most effective preventive measure that reduces the risk of influenza and post-influenza complications. It prevents influenza-related hospitalizations and deaths in 50–60% and about 80% of patients aged over 65, respectively. There is the clinical plausibility of the association between serum vitamin D (VIT D) content and viral respiratory infections. In this study, we addressed the issue of a vitamin D modulatory effect on the immune response to seasonal influenza vaccination in elderly persons. The study comprised 96 participants aged 60–75 during the 2016/17 epidemic season. After the determination of the baseline content of VIT D and anti-hemagglutinin antibodies (H1, H3, and HB), participants were vaccinated with a trivalent vaccine. The content of the anti-hemagglutinin antibodies was rechecked 4–5 weeks afterward, showing inappreciable alterations. The negative findings of this study make the influence of serum VIT D content on the immunogenicity of influenza vaccination highly unlikely in elderly persons.

Keywords

Antihemagglutinin antibodies · Immunogenicity · Influenza · Vaccination · Viral respiratory infection · Vitamin D

1 Introduction

Influenza is a communicable disease of a seasonal nature, making it a global public health problem. Influenza vaccination is the most effective prophylactic measure for the prevention of influenza virus circulation in both the general population and risk groups. According to the World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP), a notable risk group is the elderly, as the age-related deterioration of the immune function increases the danger of post-influenza complications and death. The influenza vaccination rate in the elderly is traditionally greater compared to younger age-groups, but it is highly variable. The Vaccine European New Integrated Collaboration Effort (VENICE) study revealed, between 2% and 80% of individuals aged over 65 underwent vaccination against influenza that in Europe in the 2008/

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09 season (Mereckiene et al. 2010). The Polish elderly population ranks close to the lower end of this range with about 8% of individuals vaccinated in the 2016/17 season (Łuniewska et al. 2019). The vaccination effectiveness decreases in the elderly, reaching just 17–53%, depending on the virus type of virus in a season, compared to 70% in younger age-groups (Goodwin et al. 2006). The aging process leads to a gradual loss of active immune cells and, thus, the reactivity to produce antibodies in response to vaccination. The loss approximates 30–40% past the age of 60 when compared to the individuals below 35. There also are weakened expressions of receptors and surface molecules that regulate the immune response. Diminished effectiveness of vaccination in the elderly, stemming from a weaker immune response, reduces the expected benefits (Kostova et al. 2013). Nonetheless, there is solid evidence that vaccination against influenza substantially and to a greater extent than in younger age-groups reduces the hospitalization rate, post-influenza complications, and deaths in people aged >65 (Deguchi and Takasug 2000).

25-hydroxy vitamin D [25(OH)D] (VIT D), an old hormone (Holick 2007), has pleiotropic effects due to the presence of its receptors in nearly every karyocyte. The effects include the ability to modulate the immune function, including the viral respiratory infections (Skrobot et al. 2018; Pyrżak et al. 2015; Sundaram and Coleman 2012; Berry et al. 2011; Chadha et al. 2011; Urashima et al. 2010; Ginde et al. 2009; Laaksi et al. 2007). This ability has spurred research on the plausible influence of VIT D on the body's immune responses to various vaccinations (Sadarangani et al. 2015). A meta-analysis based on 25 randomized, double-blind studies, assessing a total of over 11,000 patients across 0–95 years of age from 14 countries on 4 continents has concluded that VIT D supplementation is beneficial in preventing incidents of respiratory tract infections in the individuals unaffected and affected by past respiratory tract infections (Martineau et al. 2017).

Experimental studies have provided insights into the underlying mechanisms of reinforcing both innate and acquired immunity in response to vaccination. The mice vaccinated with inactivated influenza vaccines with simultaneous administration of 1,25-$(OH)_2$D demonstrate the enhanced cytokine production, lymphocyte proliferation, mucosal defenses, and systemic antibody production (Ivanov et al. 2006; Van der Stede et al. 2004; Enioutina et al. 1999; Daynes et al. 1996; Daynes and Araneo 1994). In contradistinction, a few clinical trials conducted so far have failed to conclusively support the experimental results. Only have two clinical trials lent some support for the increased production of antibodies in response to tetanus toxoid and BCG vaccinations concerning VIT D supplementation (Heine et al. 2011; Lalor et al. 2011). Concerning the influenza vaccination, no conclusive or null associations have been noticed in a few available studies conducted in pediatric (Sadarangani et al. 2016; Sundaram et al. 2013) and over 50 years of age populations (Science et al. 2014; Principi et al. 2013). The contentious results and a general paucity of information linking the serum content of VIT D and the immune response to vaccination against influenza in the elderly made us reinvestigate this issue in the Polish elderly population. The issue is of clinical importance in the face of the increasing, reaching over four million recorded influenza and influenza-like cases in the 2016/17 season in Poland, with a 16% increase in hospitalizations (Kowalczyk et al. 2018; Szymański et al. 2018).

2 Methods

2.1 Patients and Protocol

The study included 96 consecutive patients aged 60–75 (F/M – 61/35) receiving outpatient care between September and November 2016. Exclusion criteria were as follows: active cancer, autoimmune disorders, contraindication against influenza vaccination, acute kidney disease, liver failure, and primary hyperparathyroidism (Grohskopf et al. 2017). At the preparatory stage, 5 mL samples of blood were drawn from the ulnar vein to assess the serum content of 25 (OH)D using an electrochemiluminescent

method. Patients were stratified into two groups concerning the 25(OH)D content: < 30 ng/mL (75 nM) (n = 74), taken as the lower cut-off level of normal, and ≥ 30 ng/mL (75 nM) (n = 22). In the group with 25(OH)D deficiency, a subgroup with a severe deficiency of less than 20 ng/mL was distinguished (n = 30). To achieve a similar size of groups with and without VIT D deficiency, 22 patients were randomly picked up from the remaining 44 patients with a less severe deficiency (VIT D 20–30 ng/mL) to receive supplementation in a dose of 2000–4000 IU, depending on the body mass. After 1 month, blood samples were drawn again from all the patients to determine the baseline levels of 25 (OH)D and anti-hemagglutinin (anti-HA) antibodies. Ultimately, the group with normal VIT D level included 44 patients, while the group with deficiency included 52 patients.

All the patients were vaccinated against influenza with a single dose (0.5 ml) of the trivalent vaccine (Vaxigrip®, Sanofi Pasteur; Marcy-l'Étoile and Val-de-Reuil, France) for the 2016/17 season. One month after vaccination, another blood sample was collected from each patient to determine the anti-HA titers for the following antigens contained in the vaccine, of 15 μg each, using the hemagglutination inhibition assay:

- H1: A/California/7/2009(A/H1N1/pdm09)
- H3:A/HongKong/4801/2014(A/H3N2/)
- HB: B/Brisbane/60/2008/

The greatest serum dilution in which the agglutination of blood cells was still inhibited was taken as the anti-HA titer for a given viral strain. The following parameters were assessed and compared before and after influenza vaccination:

- Geometric mean titer (GMT);
- Mean fold increase (MFI), calculated as the GMT ratio of after/before vaccination;
- Protection rate (PROT), the percentage of patients having the anti-HA titers ≥1:40 in the serum sample;
- Response rate (RESP), the percentage of patients in whom at least a four-fold increase in antibody titers was observed following vaccination;

We used the following guidelines of the Committee for Proprietary Medicinal Products of the European Medicine Agency for the assessment of an effective serological response to vaccination in patients aged over 60 (CPMP):

- MFI ≥ 2.0
- PROT ≥60%
- RESP ≥30%

2.2 Statistical Elaboration

Data were presented as medians with 95% confidence intervals (95%CI) and counts with percentages. All data had a skewed distribution as checked with the Shapiro-Wilk test. The following non-parametric tests were used for the statistical elaboration as required:

- 1-sample fraction test with continuity correction, with the alternative hypothesis, that the population fraction is greater than 50%;
- Wilcoxon rank test with continuity correction, with the alternative hypothesis, that the position parameter in the population is different from 0;
- Wilcoxon rank pair test with correction for multiple comparisons;
- Fisher test for the 2 × 2 table, with the alternative hypothesis that the odds ratio in the population is different from 1;
- Kruskal-Wallis rank test, with the null hypothesis that the position parameter is the same in each group and the alternative hypothesis that the position parameter is different in at least one group);
- Cochran-Mantel-Haenszel Chi-square test, with the null hypothesis, that two variables are conditionally independent in each layer, assuming that there is no third-degree interaction;
- Breslow-Day goodness of fit test for kx2x2 multi-way tables.

Some variables were subjected to log transformation and the analysis was expanded by log-linear elaboration for multi-way tables. The likelihood ratio test and the Pearson Chi-square test were used for the model fit verification. A p-value <0.05 defined statistically significant differences. Statistical analysis was based on R statistical software v3.1.3.

3 Results

The immune response to influenza vaccination consisted of manifold increases in the GMT for each anti-HA titer investigated and, consequently, in the MFI, i.e., the GMT before/after vaccination ratio, in the patients with both <30 ng/mL and ≥ 30 ng/mL serum 25(OH)D content. However, the difference in the MFI between the two 25(OH)D pools was inappreciable, indicating the changes in the anti-HA titers were unrelated to the 25(OH)D level (Table 1).

The protection rate assessed as the percentage of patients having the anti-HA antibody titers ≥1:40 in the serum sample substantially increased after influenza vaccination, going way beyond the required 60% threshold of the population in case of each HA. The increases were similar in the patients with both <30 ng/mL and ≥ 30 ng/mL content. Therefore, the level of serum 25(OH)D failed to conditionally associate with the level of protective serological response to vaccination (Table 2). Likewise, there were no significant differences in the response rate, i.e., the percentage of patients in whom influenza vaccination caused a four-fold or more increase in the anti-HA antibody titers, between the groups with the 25(OH)D < 30 ng/mL and ≥ 30 ng/mL. Nor did the OR of a greater than four-fold increase in any of the anti-HA antibody titer depend on the 25(OH)D content (Table 3).

4 Discussion

Society aging generates growing costs for public health worldwide. The percentage of people aged over 60 was estimated at 8% globally in the 1950s. It reached 10% in 2000 and is prognosticated to increase to 21% in 2050 (United Nations 2012). It is thus paramount to search for ways to strengthen the protection of this vulnerable population segment against influenza infection and the related complications. The immune response to influenza vaccination is weaker in the elderly compared to younger people. Yet the elderly are at the greatest risk of severe infection course and represent a group often exhibiting VIT D deficiency. The biological plausibility arises that there might be a causal link between VIT D deficiency and the propensity for acquiring influenza infection as well as for impaired serological response to influenza vaccination in the elderly. Yet despite the incremental knowledge on the molecular mechanisms of VIT D action on the immune system function, the

Table 1 Geometric mean titers (GMT) and mean fold increase (MFI) depending on the serum 25(OH)D content in patients before and after influenza vaccination (n = 96)

	25(OH)D (ng/mL)	n	Before vaccination	After vaccination	After/Before ratio	Mean difference (log x)	W-test
			GMT (95%CI)	GMT (95%CI)	MFI(95% CI)		p
H1	< 30	52	11.01 (6.6–18.7)	90.2 (59.2–133.4)	8.2 (1.3–1.8)	2.1	0.40
	≥ 30	44	8.1 (4.7 14.2)	43.8 (23.7–77.2)	5.4 (1.2–7.8)	1.7	
H3	< 30	52	5.0 (3.0–8.4)	76.6 (44.6–133.4)	15.3 (0.8–2.8)	2.7	0.58
	≥ 30	44	8.7 (4.6–16.0)	97.7 (54.6–173.2)	11.3 (1.5–6.5)	2.4	
HB	< 30	52	16.6 (11.9–22.0)	96.4 (74.8–124.2)	5.8 (3.0–7.6)	1.9	0.87
	≥ 30	44	17.1 (12.9–22.3)	88.4 (57.2–128.3)	5.2 (2.6–6.7)	1.6	

Data are medians (95% conficence intervals); p-value denotes the comparison of the MFI values between <30 ng/mL and > 30 mg/mL 25(OH)D levels for each anti-H titer; *W-test,* Wilcoxon's rank test with continuity correction (R package)

Table 2 Protection rate (PROT), i.e., the number (percentage) of patients with the anti-HA titers ≥1:40 in the serum sample, depending on the serum 25(OH)D content in patients before and after influenza vaccination

PROT (n = 96)	25(OH)D (ng/mL)	Anti-HA titers	Before vaccination n (%)	After vaccination n (%)	OR (95%CI)	Test	Chi^2	df	p
H1	< 30	< 1:40	31 (59.6)	11 (21.2)	5.50 (2.31; 13.08)	BD	0.58	1	0.44
		≥ 1:40	21 (40.4)	41 (78.8)		CMH	21.59	1	0.00001
	≥ 30	< 1:40	27 (61.4)	14 (31.8)	1.91 (0.62; 5.88)	Pooled OR	4.35		
		≥ 1:40	17 (38.6)	30 (68.2)		(95% CI)	(2.35; 8.04)		
H3	< 30	< 1:40	37 (71.2)	12 (23.1)	8.22 (3.41; 19.84)	BD	0.49	1	0.49
		≥ 1:40	15 (28.8)	40 (76.9)		CMH	34.93	1	0.00001
	≥ 30	< 1:40	28 (63.6)	11 (25.0)	5.25 (2.10; 13.15)	Pooled OR	6.63		
		≥ 1:40	16 (36.4)	33 (75.0)		(95% CI)	(3.52; 12.50)		
HB	< 30	< 1:40	34 (65.4)	1 (1.9)	96.33 (12.28; 755.75)	BD	1.00	1	0.32
		≥ 1:40	18 (34.6)	51 (98.1)		CMH	81.86	1	0.00001
	≥ 30	< 1:40	33 (75.0)	4 (9.1)	30.00 (8.74; 103.02)	Pooled OR	47.06		
		≥ 1:40	11 (25.0)	40 (90.9)		(95% CI)	(16.48; 134.33)		

Data are counts (percent); *OR,* odds ratio; *95%CI,* 95%, confidence intervals; *BD,* Breslow-Day of homogeneity for the pooled OR; *CMH,* Cochrane-Mantel-Haenszel Chi-square test of homogeneity for the pooled OR

Table 3 Response rate (RESP), i.e., the number (percentage) of patients in whom in the anti-hemagglutinin antibody (H1, H3, and HB) titers below and above the four-fold increase cut-off level were observed following vaccination, depending on the serum 25(OH)D content

RESP (n = 96)	Anti-HA titers	25(OH)D content < 30 ng/mL n (%)	25(OH)D content ≥ 30 ng/mL n (%)	OR (95%CI)	F-test p
H1	< 4-fold	20 (38.5)	22 (50.0)	0.62 (0.26; 1.52)	0.30
	≥ 4-fold	32 (61.5)	22 (50.0)		
H3	< 4-fold	20 (38.5)	15 (34.1)	1.21 (0.48; 3.05)	0.68
	≥ 4-fold	32 (61.5)	29 (65.9)		
HB	< 4-fold	19 (36.5)	15 (34.1)	1.11 (0.44; 2.82)	0.83
	≥ 4-fold	33 (63.5)	29 (65.9)		

Data are counts (percent); *OR,* odds ratio; *95%CI,* 95%, confidence intervals; p-value denotes the comparison between the groups of patients with the serum 25(OH)D < 30 ng/mL and ≥ 30 mg/mL

research and clinical trials on the subject have yielded contentious results.

The immune cells are capable of producing 25-hydroxyvitamin D 1-alpha-hydroxylase (CYP27B1), the enzyme essential for transforming 25(OH)D to $1,25(OH)_2D$, i.e., the biologically active form of VIT D. CYP27B1 activity in the immune system does not depend on the calcium and phosphate metabolism but rather on the immune stimulus. Most immune cells of both specific and non-specific response arms have nuclear VIT D receptors (VDRs) (Chun et al. 2014). The VDRs are clearly expressed in the antigen-presenting cells (APCs) and both T and B lymphocytes. Further, many APCs produce VIT D-activating enzymes allowing local, extrarenal activation of the vitamin. VIT D stimulates differentiation of

monocytes to macrophages capable of chemotactic and phagocytic antibacterial functions (Lang and Aspinall 2015; Lang and Samaras 2012).

By far, no studies concerning a possible link between the VIT D serum content and the immunogenicity of influenza vaccinations in patients aged over 60 have been conducted in the Polish population. The findings of the presented study pointedly negate the presence of any appreciable effect of 25(OH)D content on the serological response to influenza vaccination, assessed from the level of anti-HA antibody titers in VIT D deficient when compared to non-deficient patients. The negative findings are in line with other relevant studies. In a prospective Canadian cohort study, seroprotection and seroconversion were assessed 3–5 weeks after the application of a trivalent influenza vaccine in 391 healthy children and teenagers aged 3–15. The results were compared against the initial 25(OH)D levels, without additional supplementation. The average 25 (OH)D serum level was 24.4 ng/mL and failed to relate to the degree of seroprotection or seroconversion (Science et al. 2014).

The pediatric population was also studied in 116 previously unvaccinated Italian children, aged 2–5, with recurring inner ear infections during the 2011/12 epidemiological season. They were randomly assigned to a group with oral daily VIT D supplementation of 1,000 IU and the other without supplementation. After 1 month of supplementation, the children were vaccinated twice – with an in-between interval of 1 month – using a trivalent seasonal vaccine. The findings also failed to show any changes in the anti-HA antibody production in either group (Principi et al. 2013). On the other side, Sundaram et al. (2013) have assessed the relation between VIT D content and response to influenza vaccination in the elderly. A total of 1,103 subjects aged $\geq$50 were included in the study over the 2008/09 and 2009/10 seasons. All were vaccinated with a trivalent vaccine for the respective season. The seroprotection and seroconversion were assessed 21 and 28 days after vaccination against the initial 25(OH)D levels with no supplementation. A mean serum VIT D level was 31 $\pm$ 11 ng/mL, with 25% of subjects having less than 25 ng/mL, considered deficient. The findings of that study showed no improvement in the immune response to vaccination in patients with the normal VIT D level. Likewise, another study performed in 159 healthy individuals, aged 50–74, during the 2010/11 season has failed to substantiate a relation between VIT D content and the immunological response to influenza vaccination (Sadarangani et al. 2016). However, the authors have reported a weak association of VIT D with granzyme B (GzmB), a protein belonging to the chymotrypsin family engaged in viral protein degradation, 75 days after vaccination (Jahrsdorfer et al. 2010). This protein is synthesized by cytotoxic lymphocytes and natural killer (NK) cells and in lesser amounts by CD4+ lymphocytes, basophils, and neutrophils. It has also been found in dendritic cells (Bratke et al. 2010). Currently, the most acceptable method of the assessment of immune response to vaccination is the evaluation of anti-HA antibody titers, which defines the level of seroconversion and seroprotection. However, seroconversion in response to influenza infection does not always occur in elderly individuals. The GzmB is conducive to the differentiation between influenza and influenza-like infections, regardless of humoral response (Shahid et al. 2010). The assessment of the cellular response to influenza vaccination in the elderly, measured extracorporeally via GzmB levels, shows a much better association with the immune response than that of ant-HA antibody titers (McElhaney et al. 2006; McElhaney et al. 2001). As the human body ages, the relevance of cellular immunity for protection against influenza increases (Theeten et al. 2016).

This issue of GzmB response to influenza vaccination is worthy of exploring in further research since confinement to the standard immune response consisting of anti-HA antibody titers may underline differences between the serological evaluation and the clinical effect of vaccination (Sundaram et al. 2013). Salk et al. (2013) have put forward a hypothesis that a weak response to vaccination and insufficient protection against influenza stem from the age-related unfavorable changes at the cellular response level. The basis for this hypothesis is a lack of

association between changes in anti-HA antibody titers and changes in GzmB level found in blood tests of 88 individuals, aged 50–74, vaccinated against influenza. The authors have also noticed a weak GzmB reactivity in the population studied. The present study adds up to the notion that the serum level of VIT D does not affect the immunogenicity of influenza vaccination in the elderly. There is merit in the continuing search for novel ways to increase the effectiveness of influenza vaccinations and protect the elderly against viral infections.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was accepted by the Bioethics Committee of the Wrocław Medical University in Poland.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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Influenza A (H1N1) and Respiratory Syncytial Virus (RSV) Coinfection in a Newborn Child: A Case Report

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Abstract

This paper presents a case of coinfection of influenza A virus (H1N1) and respiratory syncytial virus (RSV) in a male newborn. On the first day of life, the newborn required passive oxygen therapy, followed by respiratory support with nasal continuous positive airway pressure (nCPAP) due to respiratory insufficiency. As the newborn's respiratory effort was intensifying, he was intubated. In the second day of life, a nasopharyngeal swab was taken yielding the presence of H1N1 and RSV in the RT-PCR test. The child was isolated and given oseltamivir and empirical antibiotic therapy, which improved his condition. Other newborns who initially stayed with the sick child in the post-delivery room did not obtain oseltamivir prophylactically as their nasopharyngeal swabs were negative. The child's parents denied the occurrence of influenza-like symptoms within 14 days of delivery, which suggests a transplacental transmission of the child's infection or asymptomatic course of infection in the parents. In conclusion, this report confirms the possibility of viral coinfections in newborns, which points attention to considering a panel of respiratory viruses in the diagnostics. Symptoms of influenza in newborns may be atypical, including a fever-free course. Oseltamivir treatment in newborns with influenza seems an effective therapeutic measure.

Keywords

Coinfection · Influenza · Newborn · Nasopharyngeal swab · Respiratory syncytial virus

1 Introduction

Influenza is an acute infectious disease caused by a virus from the Orthomyxoviridae family. It is mainly spread by droplet and contact transmission. The World Health Organization (WHO) estimates that 5–15% of the global population suffers from influenza every season, which corresponds to 3–5 million cases with about 500,000 deaths related to influenza and its complications (WHO 2018). Children, in particular those under the age of 5, present a reservoir of influenza viruses and the incidence is in this age group is highest (Wang et al. 2020). The global mortality associated with influenza in children under 5 years of age was estimated at 28,000 to 111,500 cases in 2008, with deaths reported nearly exclusively in poor and developing

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countries (Nair et al. 2011). Data on the influenza epidemiology in young children, infants up to 6 months of age, and newborns are scarce and they come mainly from the United States, where the estimated number of influenza-associated hospitalizations of children up to 5 years of age is about 900,000 a year, including 228,000 hospitalizations of infants under 6 months (Nair et al. 2011). In the United States, the cumulative influenza incidence was 44 hospitalization per 100,000 children aged under 5 years in the 2016/2017 season. Wang et al. (2020) have concluded that 23% of children's hospitalizations can be associated with influenza and 36% of deaths among infants under 6 months of age with influenza and its complications.

It has been believed for many years that newborns are unaffected by an influenza virus infection because they are protected by transplacentally acquired antibodies and are exposed to a rather small number of social contacts associated with infection transmission (Puck et al. 1980). Reports on influenza in newborns are scarce. Wilkinson et al. (2006) and Sert et al. (2010) have reviewed influenza cases in prematurely born infants and show that the infection course is either asymptomatic or severe; in the latter case, it may involve respiratory failure and death. These authors have also described influenza outbreaks in neonatal units. Due to the rarity of influenza in newborns and rather ill-defined disease course, this report presents a case study of coinfection of influenza A (H1N1) virus and respiratory syncytial virus (RSV) in a newborn child. To the best of our knowledge, this is the first description of such coinfection in a newborn child.

2 Case Report

A male newborn from second pregnancy but the first childbirth. The first pregnancy ended in miscarriage. The newborn was delivered in the 38th week of pregnancy by C-section due to premature drainage of amniotic fluid and uterine fibroids. The birth weight of 3.245 g and an average general condition, Apgar score of 7-7-9-10. At birth, he required suctioning and assisted breathing with a Neopuff resuscitator to provide positive pressure ventilation (Fisher & Paykel Healthcare GmbH, Schorndorf, Germany). A *Streptococcus agalactiae* test gave a negative result and the umbilical artery blood gas content was normal. The baby was moved to the observation unit and placed in an incubator. A physical examination revealed skin pallor, slight tenderness, lung crackles on auscultation, respiratory effort in the form of expiratory grunting, systolic murmur (1–2/6 on the Levine scale). The parenchymal organs in the abdominal cavity were of normal size. Peripheral capillary O_2 saturation decreased 75%, which necessitated the implementation of supplemental oxygen therapy of inspiratory fraction of oxygen (FiO_2) of 0.4. Capillary blood gasometry was the following: pH 7.29, PCO_2 55.4, HCO_3^- 22.1 mM, and BE 2.4 mM.

Due to threatening respiratory failure, the baby was transferred to the intensive care unit. He was connected to the respiratory support with nasal continuous positive airway pressure (nCPAP). The resulting clinical improvement enabled a reduction of supplemental oxygen concentration to FiO_2 of 0.25. The levels of interleukin 6 (IL-6) and C-reactive protein (CRP) were increased; 525.2 pg/mL (normal range: 0.0–9.7) and 0.9 mg/L (normal range: 0.0–5.0), respectively. The leukocyte count was with the normal range – 15.1×10^9/L (normal range: 9.0–30.0 $\times$ 10^9/L). Bilateral interstitial inflammatory infiltrates were found in a chest X-ray. Empirical antibiotic therapy consisting of ampicillin and gentamicin and enteral feeding with mother's milk was initiated. In the following hours, respiratory support with nCPAP continued. Nonetheless, increasing respiratory effort and demand for oxygen (FiO_2 of 0.4), anxiety, posseting, and periodic saturation dips were present. The access to the umbilical vein was made to begin trophic nutrition. At this stage, blood leukocyte count increased to 24.1×10^9/L, with a stable gasometry profile.

At the end of the first day of newborn's life, there was no clinical improvement and respiratory acidosis was observed, necessitating the intubation, mechanical synchronized intermittent mandatory ventilation (SIMV) with peak inspiratory pressure

(PIP) +23 cmH_2O, positive end-expiratory pressure (PEEP) +4 cmH_2O, FiO_2 of 0.6–0.5, and sedation with fentanyl in a dose of 1–5 μg/kg/h in a continuous drip, depending on the pain scale result. The measure undertaken led only to a temporary improvement of the condition. Therefore, the ventilatory parameters used were upwardly modified, with the maximum FiO_2 of 0.7 and a breathing rate of 60–75 *per* min. Blood pressure was at a normal level throughout, no signs of circulatory failure were observed, and blood gas content remained stable. Repeated chest X-ray showed bilaterally decreased lower lung aeration and a small right pneumothorax that did not require pleural drainage. Blood cultures remained negative. The echocardiographic screening showed a patent foramen ovale and normal structures of the heart and large vessels according to the baby's age. The leukocyte index, i.e., the mean ratio of immature to total neutrophils (I/T), was in the normal range of <16 as were the levels of serum transaminases. The serum gamma-glutamyltranspeptidase (GGTP) (154.0 U/L) and procalcitonin (PCT) (8.8 ng/mL) were moderately increased. The following PCT apportioning was considered: < 0.5 ng/mL – low risk of early bacterial infection or possible local infection; 0.5–2.0 ng/mL – possible systemic bacterial infection, recommended control test within 6–24 h; and > 2.0 ng/mL – probable systemic infection or sepsis. The general condition of the baby was rather severe but stable on the second day of life, with no tendency to improve. An ultrasound transdermal examination and the abdominal cavity examination were performed, both showing no abnormalities. Any cardiological causes of the health condition, particularly a congenital heart disease or pulmonary hypertension, were excluded as well. Suspicion of infection of viral etiology arose due to the current presence of the epidemic influenza season. The suspicion was strengthened by the ambiguous clinical picture, no symptoms of a defined perinatal infection, and an unclear medical history of the mother. However, a rapid diagnostic test for the respiratory syncytial virus (RSV) was negative.

Swabs were taken from both nostrils for the polymerase chain reaction (PCR) examination of 12 respiratory viruses, including influenza, parainfluenza 1,2,3,4, human metapneumovirus, adenovirus, rhinovirus, coronaviruses 229E/NL63 and OC43/HKU1, enterovirus, and RSV. The examination confirmed the presence of the genetic material of influenza A virus and RSV. The decision was made to continue the antibiotic therapy for another 7 days despite a negative blood culture, which could have to do with too short a microbiological incubation period. In the meantime, the causal treatment with oseltamivir, a neuraminidase inhibitor, was implemented in a dose of 2 mg/kg daily, bid, for 5 days. The baby was isolated but the mother's visits were allowed observing strict sanitary regimes. The baby's condition started improving gradually and he was extubated on the fifth day of his life. Respiratory support was altered to a noninvasive nCPAP with the FiO_2 of 0.35–0.23. Only was slight physiological jaundice noticed. The enteral nutrition was gradually increased, first with a tube and then with a feeding teat. On the sixth day of life, respiratory support and parenteral nutrition were terminated and the umbilical vein catheter was removed. From the eighth day, the baby was breastfed, with a modified milk supplement. Complete blood count, white cell smear, CRP, and acid-base balance all showed no irregularities. The biochemical markers of potential heart muscle damage such as troponin, phosphocreatine kinase, and CK-MB were within the normal limits.

On the first day of life, the baby was vaccinated against hepatitis B and was subjected to metabolic and hearing screenings. BCG vaccination was postponed for 2 weeks after discharge from the hospital due to a severe course of the infection. The baby was discharged after 12 days in a good general condition and a weight gain of up to 3302 g. A control visit in a neonatal outpatient clinic was recommended 1 week after discharge and a temporary ultrasound examination 2 months later. Additionally, control audiological, ophthalmological, and cardiological examinations were scheduled for the near future.

Two other prematurely born neonates who stayed in the same post-delivery room were closely monitored for disease symptoms and had nasal and throat swabs taken for the PCR tests for

the presence of influenza virus and RSV. The genetic material of RSV and enterovirus was identified in one, whereas the other tested negative. Neither child showed any disease symptoms related to influenza or coinfection. These newborns were discharged from the hospital when they reached the minimum weight of 2000 g, had no sign of infection, did not have desaturations or apneic episodes, and were mature enough to draw breast milk or be bottle-fed.

3 Discussion

The case of symptomatic influenza A (H1N1) in a male baby born at term, presented in this paper, is one of a few ever reported. The notable features of this case were the early onset of symptoms on the day of birth, a mismatch between a fever-free course and increasing respiratory insufficiency that necessitated the intubation and respiratory support, and no influenza-like symptoms in the mother and her immediate environment during the perinatal period. The baby's nasopharyngeal sample was positive for the genetic material of influenza A (H1N1) virus. The diagnosis of influenza was confirmed by a significant improvement after the implementation of oseltamivir treatment. However, the nasopharyngeal sample also tested positive for the respiratory syncytial virus (RSV), which points to a coinfection. Coinfections with respiratory viruses have previously been reported but the severity of symptoms appears to be independent of the number of etiological factors (Pichler et al. 2018). In the literature, there are single descriptions of influenza cases in the first hours of life, whereas symptomatic cases of RSV concern newborns aged 5–282 days (58 days on average) and mostly are nosocomial infections related to epidemic outbreaks in intensive care units for premature babies (Pichler et al. 2018). The RSV alone infections, notably, have a favorable course with low mortality, which makes the disease similar to the influenza of the neonatal age (Marcone et al. 2018; Reese et al. 2016; Reid et al. 2011).

The first description of pneumonia caused by influenza A (H1N1) in a baby born from a full-term uncomplicated pregnancy newborn was reported by Sert et al. (2010). In that case, the parents had reported influenza-like symptoms 2 weeks before delivery. There were also other differences in the infection course when compared with the case reported in the present report. The infection appeared on the 6th day after birth, and it was highly symptomatic with fever, bilateral crackles on auscultation, interstitial bilateral inflammatory lung changes in X-ray, and increased serum CRP. Sepsis was excluded based on negative blood and urine cultures. Empirical antibiotic therapy consisting of cefazoline and gentamycin was implemented, which was ineffective. Since viral etiology was then confirmed, oseltamivir was added on to the antibiotic treatment, which improved the baby's condition.

Other reports concerned outbreaks of influenza infection in prematurely born babies in intensive neonatal care units during the pandemic of 2009/2010. Milupi et al. (2012) have reported an outbreak of influenza A in the UK where three newborns aged 13–28 days became ill. The predominant symptoms were bradycardia, desaturation, tachypnea, and apnea. Tsagris et al. (2012) have reported a similar outbreak in Greece where three newborns aged 47–84 days became ill, with the symptoms of runny nose, fever, and apnea. Rocha et al. (2010) have reported influenza in 12 newborns aged 3–38 days in Portugal, in whom deterioration of respiratory function necessitated the initiation of mechanical ventilation. Another two influenza A outbreaks took place in the United States. In one, influenza A was diagnosed in three prematurely born babies aged 16 to 51 days, with the symptoms of lung crackles, apnea, desaturation, and convulsions, which necessitated the artificial ventilation (Vij et al. 2011), In the other, Pannaraj et al. (2011) have reported influenza was reported in 11 newborns aged 5–192 days, with fever, desaturations, and other typical respiratory symptoms as outlined above. In all those reports, oseltamivir treatment was implemented in each newborn, regardless of the time that had elapsed since the occurrence of symptoms, and the treatment was effective. There were other single cases of influenza in newborns reported. One such case was in Israel where a baby born at 32 weeks

developed the symptoms of respiratory failure on the 50th day of life. After a course of oseltamivir treatment, the child was discharged from the hospital in a good condition 10 days later (Barak et al. 2010). The other was in India where a baby also born at 32 weeks developed the symptoms of respiratory failure on the 6th day of life. Influenza A (H1N1) was diagnosed 4 days later and oseltamivir treatment was implemented. In this case, the treatment was ineffective and the baby died after a week (Jajoo and Gupta 2010). Noticeably, however, the influenza mortality rate in newborns is very low, which distinguishes this age-group from infants and the elderly. The reasons behind this phenomenon are unknown, but it is usually ascribed to better care and closer supervision in intensive care units, where newborns with influenza are treated (Pichler et al. 2018). The anti-epidemic measures, akin to those used in the present report, such as patient isolation, withholding of family visits, and close observation of other babies who could have been in contact with the sick, were implemented. In the present case, no pharmacological post-exposure prevention in babies who were in contact with the sick one was used, whereas in some of the previous reports such prevention was used (Pannaraj et al. 2011; Rocha et al. 2010). The sources of infection, whenever identifiable, were unvaccinated medical staff and sick members of the children's immediate family. In the present case, the source of the influenza infection could not be identified. There was no influenza infection or any respiratory symptoms in the baby's parents in the 2 weeks preceding the delivery. Therefore, there were two possible origins of the infection: asymptomatic infection in the parents with transmission to the baby or vertical transmission from mother to baby during the time just before and after birth across the placenta, the breast milk, or through direct contact about the delivery.

Contagions, e.g., human immunodeficiency virus, can be vertically transmitted. Lincoln et al. (2017) have revealed the possibility of asymptomatic influenza virus transmission in 11% of patients. A prevalence of 16% of asymptomatic transmission has been reported by Leung et al. (2015). Asymptomatic individuals shed the influenza virus in smaller amounts and shorter time when compared to symptomatic patients but the time of shedding is a source of infection (Pichler et al. 2018). During the influenza A (H1N1) pandemic of 2009, the possibility of transplacental transmission has been reported. Valvi et al. (2010) have reported a case of a child who was born at 22 weeks to a mother with virologically confirmed symptomatic infection caused by influenza A (H1N1). Delivery was performed by C-section, the newborn was isolated from the mother immediately afterward, and oseltamivir treatment was initiated. In the 5th hour of life, the newborn showed symptoms of acute respiratory failure. The RT-PCR of nasopharyngeal swabbing confirmed the presence of the genetic material of the H1N1 pdm09 virus. Picone et al. (2011) have also indicated the possibility of vertical transmission of influenza virus in a case of a virologically confirmed infection in a child born to a mother with symptomatic influenza treated with oseltamivir. Likewise, the delivery was performed by a C-section. Although the newborn was in contact with the mother only for a few seconds, the sampling performed in the 4th hour of life confirmed the presence of the influenza A (H1N1) virus. On the other side, however, Irving et al. (2000) have failed to confirm the vertical transmission of influenza virus in a cohort study on women who contracted influenza in the second or third trimester of pregnancies. The paired pre-post natal cord sera of the women were negative for influenza A virus-specific IgM.

4 Conclusions

Viral etiology should be considered in the differential diagnosis of respiratory infections in newborns. Viral coinfections in newborns also are possible. Therefore, the diagnostics should include a panel of respiratory viruses. Symptoms of influenza in newborns may be atypical, including a fever-free course but the presence of respiratory insufficiency necessitating the initiation of mechanical ventilation. Transplacental

transmission of the influenza virus cannot be excluded in newborns. Oseltamivir treatment of influenza seems to be effective in newborns.

Conflicts of Interest The authors declare no conflicts of interest concerning this article.

Ethical Approval All procedures performed in studies involving human participants were compliant with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The paper was accepted by a Review Board of Warsaw Medical University in Poland.

Informed Consent Written informed consent was obtained from the parents of the newborn baby presented in this case report.

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Thoracic Manifestation of Granulomatosis with Polyangiitis: A Case Report

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Abstract

Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated disorder with necrotic vasculitis of small- and medium-size arteries and veins. In the literature, there are many case reports of patients with GPA of different, sometimes unusual, clinical manifestations. In this paper, we present difficulties that accompanied the process of diagnosing GPA in a 54-year-old symptomatic patient who was. Computer tomography scans showed numerous tumor-like lesions of various and irregular sizes in both lungs. Positron emission tomography scans suggested a lymphoproliferative disease, otherwise failing to provide a clue concerning its nature or localization. After a series of diagnostic twists and turns, inclusive of bronchoalveolar lavage, cervical mediastinoscopy, paratracheal lymph biopsy, and histopathologic examinations, and other tests, the diagnosis of GPA was established as the most probable. The patient was acutely treated with loading doses of methylprednisolone and cyclophosphamide, gradually tapered off during the long-term follow-up. He was discharged from the hospital in a good condition. We conclude that GPA is an uncommon disease with indistinctive signs, which raises the risk of its being overlooked. A diagnostic algorithm is required for patients with suspected GPA. A timely diagnosis is essential as the disease may quickly progress into renal or multiorgan dysfunction, and ultimately lead to death if untreated. Pulmonary involvement may also suggest neoplastic changes.

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Keywords

Antineutrophil cytoplasmic antibody · Granulomatosis with polyangiitis · Lung lesions · Nodules · Vasculitis

1 Introduction

Granulomatosis with polyangiitis (GPA, Wegener's granulomatosis) is an antineutrophil cytoplasmic antibody (ANCA)-associated disorder with necrotic vasculitis of small- and medium-size arteries and veins. The course of illness differs between the patients, but in most cases, it appears in the upper respiratory tract, lungs, and kidneys, although other tissues or organs may be affected. Each year, there are 2.1–14.4 new cases per million people diagnosed in Europe, but other sources report the prevalence is even five times higher (Yates and Watts 2017; Greco et al. 2016). According to the American College of Rheumatology, the diagnostic criteria for the classification of GPA are granulomatous inflammation on biopsy, oral ulcers, nasal discharge, abnormal findings on the chest radiograph like nodules, cavities, and fixed infiltrates, and abnormal urinary sediment consisting of red cells casts or more than five red blood cells per high power field (Leavitt et al. 2010). The presence of two or more abnormalities is associated with a high possibility of the disease. ANCA antibodies play a role in recognition but are not decisive in the diagnostic process due to relatively low sensitivity. Herein we report diagnosing difficulties concerning the GPA.

2 Case Report

In March 2017, a 54-year-old male was admitted to the Department of Internal Medicine of the Fourth Military Teaching Hospital in Wroclaw, Poland due to cough, chronic fever of 38-40 °C accompanied by nausea, vomiting, and dripping sweat. The patient presented a history of 3 months of severe dry cough with breathlessness. He was treated empirically in an outpatient clinic with broad-spectrum antibiotics, which was of no avail. The patient was having type II diabetes, erosive gastropathy, colon diverticulosis, psoriasis, and a focal thyroid lesion in the right lobe. The ear-nose-throat (ENT) examination showed a left-sided polyp between the middle and inferior nasal concha. The patient's general condition was poor at admission. A chest X-ray showed several round shadows of about 15 mm in diameter in the right lower pulmonary field (Fig. 1). Computed tomography (CT) examination showed numerous tumor-like lesions of irregular size in both lungs

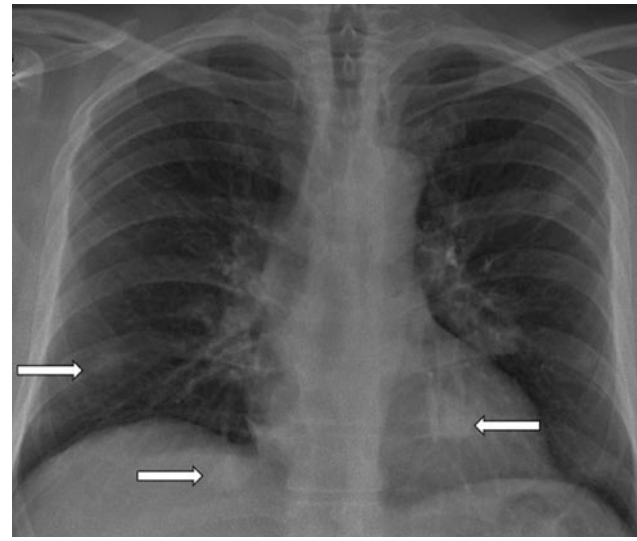

Fig. 1 Chest X-ray showing round bilateral opacities in the lungs

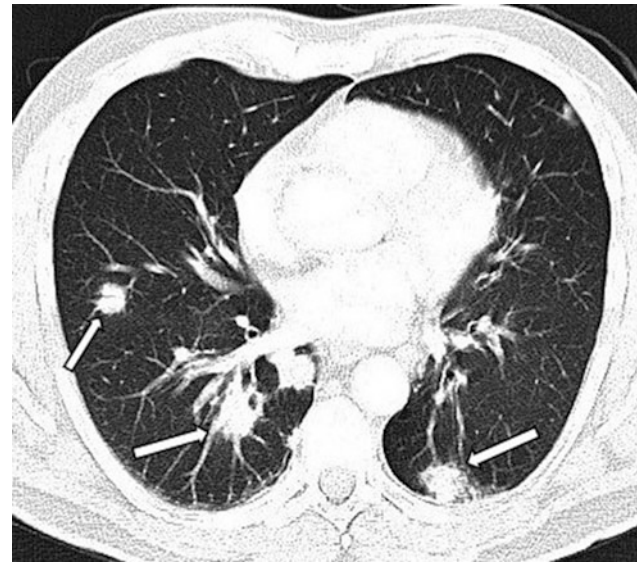

Fig. 2 Computed tomography (CT) scan of the chest showing nodular shadows in lung parenchyma (marked by arrows)

that suggested neoplastic infiltrations (Fig. 2), but without any diagnostic conclusion. The transthoracic needle biopsy and bronchoscopy remained diagnostically inconclusive. Bronchoalveolar lavage (BAL) revealed numerous neutrophils (71.0%), lymphocytes (18.0%), and an insignificant number of bacteria like *Streptococcus oralis, Neisseria* spp., *Escherichia coli*, and *Streptococcus salivarius* with a reduced number of macrophages (11.0%). *Mycobacterium tuberculosis* was not present in the culture.

The antinuclear antibody (ANA) panel was negative. Unfortunately, ANCA tests were not performed at this stage. Positron emission tomography (PET) confirmed the presence of an active proliferative process, but it failed to localize the primary neoplasm. The scans suggested an extension of diagnostics toward the lymphoproliferative disorder. Therefore, cervical mediastinoscopy was performed under general anesthesia. The paratracheal lymph nodes (station 3) and right lower paratracheal nodes (station 4R) were harvested. However, histopathological examination revealed normal lymphoid tissue without any malignancy. The open lung biopsy was considered, but the patient's general condition was too poor to perform an invasive procedure.

As the patient was suspected of tuberculosis, having cough and general malaise, he was admitted to the Pulmonary Division at the end of April 2017. A repeated X-ray showed several tubercles in both lungs. Symptomatic treatment was implemented consisting of ibuprofen, dalteparin, megestrol, and paracetamol with tramadol. Additionally, metformin was given to control diabetes. Based on medical history, documentation, X-ray examinations, and a consultation by an experienced pulmonologist, the GPA was highly suspected.

The patient's condition was deteriorating, and after a conclusive exclusion of neoplasm, he was referred to the Department of Rheumatology at Wroclaw Medical University. He had problems with keeping a vertical body position due to the progressing general malaise. C-reactive protein and the erythrocyte sedimentation rate were increased. Signs of renal impairment appeared consisting of protein 0.5 mg/dL (norm: 0.0–0.2 mg/dL), white blood cells 5–8 (norm: 0–5), and erythrocytes 9–13 (norm: 0–3) per high power field in the urine. ENT consultation and CT imaging showed polyps whose histopathological examination was unremarkable. Since the deterioration of the patient's condition accelerated, steroid treatment was implemented. Methylprednisolone (1 g/day) and cyclophosphamide (1.2 g/day) were administered intravenously for 3 days accompanied by 2-mercaptoethanesulfonate sodium (Mesna;

0.72 g/day) for protection of the urinary bladder against inflammation. The patient's condition and inflammatory biochemical indices improved. Then, oral methylprednisolone was continued in a dose of 52 mg/day, divided into 32 mg at 8 am, 16 mg at 11 am, and 4 mg at 1 pm. The total dose was gradually tapered off to 48 mg/day after 1 month and 40 mg/day after another month. Treatment consisting of six infusions of cyclophosphamide in a dose of 0.75 mg/kg every 4 weeks also was prescribed. However, steroid therapy worsened hyperglycemia, which required the introduction of insulin therapy. Additionally, trimethoprim-sulfamethoxazole in a dose of 480 mg bid was given for 5 months. Results of tests and cyclophosphamide courses are depicted in Table 1. Since the diagnosis of GPA was not confirmed by histopathology, the patient was scheduled for a monitoring chest CT examination 3 months after discharge.

3 Discussion

The GPA is a multisystem disease that has many faces, ranging from rhinosinusitis and cough to renal and lung involvement (Comarmond and Cacoub 2014). It is prevalent in Caucasians, with about equal gender distribution (Lutalo and D'Cruz 2014). The onset most often occurs at the age of 45–60 but may appear at another age as well (Filocamo et al. 2017). The pathophysiological mechanism involves necrotizing vasculitis of small- and medium-sized arteries and veins with intra- and extra-vascular granulomas that are most common in the upper and lower respiratory systems (Savage et al. 2000). Diagnostic criteria for GPA are based on clinical manifestations like inflammatory consolidations in chest X-ray, oral and nasal inflammatory lesions, and abnormal urinary sediment.

Table 1 Diagnostic tests and the main treatment course in a patient with granulomatosis with polyangiitis (GPA)

Date	ESR (mm/h)	CRP (mg/L)	ANA	cANCA (RU/mL)	Computed tomography	Cyclophosphamide
March 2017	84	34.7	Negative			
April 2017	80	43.0				
May 2017	93	44.4	Positive	83.4		I infusion
June 2017	2	0.7				II infusion
July 2017	3	1.2				III infusion
August 2017	4	1.0			Subpleural nodules (5 mm) in VI pulmonary segment; post-inflammatory densities	IV infusion
October 2017	25	11.5				V infusion
November 2017	9	2.9	Negative	2.0		Treatment terminated
January 2018	3	0.5		2.0	Tree-in-bud signs subpleural nodules post-inflammatory densities	
January 2019	2	1.5		2.0	Regression of changes	
April 2019	4	0.53				
September 2019	2	0.18		2.0	No focal changes	

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibodies, *cANCA* antineutrophil cytoplasmic antibodies

Herein, we presented the diagnostic workup of a patient whose clinical history at presentation was hardly suggestive of GPA. Additionally, it appears there is no distinct procedure algorithm for GPA-suspected cases, which complicates and delays the workup, notably when there is a need to differentiate a nature of tumor-like mass in the lungs visualized in X-rays. In such cases, tuberculosis, neoplasm, GPA, rheumatoid arthritis, and other illnesses should be considered. In the presented report, cough, breathlessness, enlarged mediastinal nodules, a chronic febrile state with accompanying nausea, vomiting, and dripping sweat were notable at the first admission. However, cough is present, on average, in a minority 34% of patients with GPA, which makes it hard of a diagnostic value. The X-ray and CT scans showed several round shadows in the lungs. To rule out tuberculosis, the bronchoalveolar lavage was microbiologically tested. However, no mycobacteria were cultivated. The PET scan gave a false positive outcome suggesting neoplasm, albeit giving no clue to its localization. Doctors became misled to search for the primary origin of neoplasm. Mediastinoscopy was performed and numerous specimens of lymphatic nodes were examined for histopathology but failed to conclusively set the diagnosis of neoplasm. The patient's mistaken declaration that the polyp-like mass between nasal conchae detected at the ENT examination had been an inborn lesion further impeded the making of a correct diagnosis. Acquired abnormalities in the nasal cavity are often symptomatic for the GPA (Comarmond and Cacoub 2014; Masiak et al. 2017). The exclusion of neoplasm and nonconfirmation of tuberculosis has strengthened the probability of GPA, which was confirmed by positive cANCA antibody tests, and the patient was finally treated in the Rheumatology Ward as of May 2017. Abnormalities in the urine test were suggestive of kidney involvement in the form of glomerulonephritis, which is a frequent accompaniment of GPA. The immunosuppressive and anti-inflammatory treatment consisting of cyclophosphamide and methylprednisolone was commenced, leading to a prompt improvement in the patient's condition. Trimethoprim-sulfamethoxazole was added to eliminate the microbes that could potentially underlie the disease (Hasan et al. 2019).

We conclude that GPA is an uncommon disease with symptoms and signs of little specificity, making the diagnosis difficult and raising the risk of overlooking. There is a strong need for a diagnostic algorithm for patients with suspected GPA, notably in cases suggesting pulmonary neoplastic changes. Time is of paramount essence in diagnosing GPA because the disease may rapidly progress into glomerulonephritis with renal failure or multiorgan dysfunction with the ultimate death.

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Conflicts of Interest The authors declare no conflicts of interest concerning this article.

Ethical Approval All procedures performed in this study involving a human participant followed the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Wroclaw Medical University in Wroclaw, Poland.

Informed Consent Written informed consent was obtained from the patient presented in the article.

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The Natural Course of Impaired Fasting Glucose

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Abstract

Impaired glucose regulation, including diabetes and prediabetes, poses a huge global problem not only in health but also in the epidemiological and economic areas. These disorders are often detected too late or remain unrecognized. The article aims to provide a review of the prevalence, etiology, and natural history of impaired fasting glucose (IFG). We focus on the progression of isolated IFG to full-fledged type 2 diabetes and the factors conducive to the development of diabetes. The knowledge about it could help design an optimal management program for the prevention of diabetes in patients with IFG; a program that would be patient-tailored and based on the underlying pathophysiology.

Keywords

Diabetes · Impaired fasting glucose · Prediabetes · Prevention · Public health

1 Introduction

Carbohydrate metabolism disorders, including type 2 diabetes mellitus and prediabetes, pose a huge global problem not only in health but also in the epidemiological and economic areas. These abnormalities are often detected too late or remain unrecognized. Prediabetes is defined as an intermediate state between normal blood glucose levels and diabetes. The term includes such disorders as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or raised glycated hemoglobin (HbA1c), each different in the underlying pathophysiology but each associated with a higher risk of developing diabetes. It is estimated that the presence of a prediabetic state increases the average risk for the future development of type 2 diabetes by threefold to tenfold (Garber et al. 2008). Early detection of prediabetes may prevent or delay the development of diabetes and its complications.

Risk factors for the development of type 2 diabetes are established. Nonetheless, it is hard to describe the natural course of prediabetes. Data on the long-term risk of progression from prediabetes, particularly IFG, to full-fledged diabetes and the associated risk factors are still lacking or

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inconsistent. The inconsistency results from a variety of inclusion criteria and methodologies used in the available studies. Moreover, the patient cohorts often are highly heterogeneous, with no clear distinction between each prediabetic state, such as isolated IFG, IGT, or both combined. Based on a review of the current literature (Wen et al. 2017; Buysschaert et al. 2016; Chan et al. 2009; Toshihiro et al. 2008; Abdul-Ghani et al. 2006; DeFronzo 2004), it seems there is a need for a better savvy of the etiopathogenesis of IFG and the identification of factors bearing on the progression to diabetes.

2 Definitions and Diagnosis

In 1997, the American Diabetes Association (ADA) defined IFG as an elevated fasting plasma glucose (FPG) level 6.1–6.9 mmol/L (110–125 mg/dL). Six years later, the cutoff level for IFG was lowered to 5.6 mmol/L (100 mg/dL) by the ADA (Nathan et al. 2007) and the International Expert Committee (Gillett 2009; Forouhi et al. 2006), to maximize sensitivity and specificity for predicting diabetes mellitus. Nonetheless, the WHO and the International Diabetes Federation still uphold the 6.1–6.9 mmol/L cutoff glucose recommendation (WHO 2006). In isolated IFG, a 2-h post-load glucose level in the 75 g oral glucose tolerance test (OGTT) is within the normal range (below 7.8 mmol/L), in contrast to IGT, where the 2-h plasma glucose is in a range of 7.8–11.0 mmol/L (140–199 mg/dL) during OGTT.

Prediabetic diagnostic threshold and its verifying tools are still discussed (Huang et al. 2016; Buysschaert et al. 2016). Generally, FPG is used as a screening test for diabetes. OGTT is recommended in patients with a high risk of developing type 2 diabetes mellitus. Elevated HbA1c can be used as another tool for diagnosing prediabetes and diabetes, without distinction between IFG and IGT. According to the ADA guidelines, HbA1c in a range of 5.7–6.4% (39–46 mmol/mol) is considered as prediabetes (ADA 2020), whereas Canadian (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018), British guidelines (Chatterton et al. 2012) have established a higher cutoff point of 6.0 to 6.5% *(*42–47 mmol/mol*)*. The WHO has not approved the HbA1c as a diagnostic screening tool for prediabetes (WHO 2011).

3 Epidemiology

According to the last report of the Centers for Disease Control and Prevention, one in three American adults has prediabetes, mostly men, which approximates 88 M people as of 2018. The prevalence rises with age, reaching nearly 50% in those over 65 years of age. There is no significant difference between races and ethnicities (CDC 2020). The National Health and Nutrition Examination Surveys (NHANES) reported that the overall prediabetes prevalence, based on the FPG and HbA1c, increased from 27.4% in 1999–2002 to 34.1% in 2007–2010. On the other side, the prevalence of IFG remained a little changed amounting to 23.9–26.6% in 1999–2010 (Bullard et al. 2013) and 28.3% in 2011–2014 (Menke et al. 2018). The FPG above the threshold occurred more frequently in men than women, in non-Hispanic whites than in non-Hispanic blacks, and in obese subjects.

Statistically, IFG (defined as FPG 6.1–6.9 mmol/L) is rarer than IGT. In epidemiological studies in different adult populations, the prevalence of IFG ranged widely from 4.7% in Pima Indian adults (Gabir et al. 2000a) to 12.2% in Mexican-Americans (Harris et al. 1998), whereas IGT was prevalent from 11.1% in the Australian population (Dunstan et al. 2002) to 19.4% in Mexican-Americans. Based on the DE CODE Study Group (2003) and Qiao et al. (2003) studies, tallying data from 13 European and 11 Asian studies performed in subjects aged 30–89, IFG appeared more often in men than in women, mostly in young and middle-aged men, whereas IGT was common particularly in women and elderly subjects above 70 years of age. The prevalence of IFG reached a plateau in middle-aged subjects (40–50 years) in most populations. Conversely, the 2 h FPG concentration and, thus,

the prevalence of IGT increased linearly with age (DECODE Study Group 2003; Unwin et al. 2002). Notably, IFG was defined as FPG 6.1–6.9 mmol/L in all the studies above outlined.

A twofold to fourfold increase in IFG prevalence, the larger increases in younger age-groups, has been reported after the redefinition of IFG by ADA, compared with the WHO recommendations (Pankow et al. 2007; Forouhi et al. 2006; WHO 2006). A lowering of the cutoff point for IFG resulted in a nearly 20% increase in the prevalence of isolated IFG and a notable decrease in the prevalence of the isolated IGT. Thus, isolated IFG has become the most common form of a prediabetic state in both Caucasian and Asian cohorts. According to both 1999 WHO and 2003 ADA classifications, the prevalence of isolated IFG is significantly higher in Caucasians than in Asians. As a possible reason, the authors indicate a western-type diet rich in fats and meals with a high glycemic index, but this notion remains to be verified (Yip et al. 2017). In a recent meta-analysis of 46 studies performed in the general population of developed European countries, the overall prevalence of impaired glucose regulation was rated at 22.3%, and the mean prevalence of IGT was 11.4%, with no clear gender differences. In contrast, IFG occurred more frequently in men than in women, with a mean prevalence of 8.4% (Eades et al. 2016).

4 Differences Between Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) Resulting from Pathophysiology

The IFG and IGT have a significantly different pathophysiologic background. Subjects with isolated IFG have moderate insulin resistance in the liver, disturbed first-phase insulin secretion, and normal muscle insulin sensitivity. The hepatic insulin resistance leads to excessive fasting glucose production and impaired suppression of liver glucose output, resulting in basal hyperinsulinemia. In comparison, individuals with isolated IGT have moderate or severe muscle insulin resistance, impaired first- and second-phase insulin secretion, and reduced β-cell sensitivity to glucose. The muscle insulin resistance results in disturbed glucose uptake after a meal rich in carbohydrates, leading to postprandial hyperglycemia (Wilson 2017; Buysschaert et al. 2016; DeFronzo and Abdul-Ghani 2011; Abdul-Ghani et al. 2006; DeFronzo 2004). Waist circumference (>102 cm for men and > 88 cm for women) and triglyceride/HDL-C ratio (>3.5 for men and > 2.5 for women) are useful indirect indices to identify prediabetic insulin resistance (Gagliardino et al. 2018; Salazar et al. 2013; Alberti et al. 2009).

Interestingly, increased glucose level, reduced insulin sensitivity, and defects in insulin secretion might be seen as early as 13 years before the development of type 2 diabetes (Tabák et al. 2012; Tabák et al. 2009). β-cell dysfunction is also observed, even when FPG remains within a normal range (Kahn et al. 2006; WHO 2006). Given the discordant findings in autopsy (Wen et al. 2017; Butler et al. 2003) and hyperinsulinemic-euglycemic clamp studies (Basu et al. 2013; Perreault et al. 2008), the clinical relevance of these results needs further elucidation. As the categories of impaired glucose regulation often coexist to an extent (DeFronzo and Abdul-Ghani 2011; DeFronzo 2004), we can distinguish isolated IFG, isolated IGT, and a combination of the two. The DECODE and DECODA studies show that a third of the European and Asian populations with IFG, defined according to the current ADA definition as FPG 6.1–6.9 mmol/L, have the coexisting IGT (DECODE Study Group 2003; Qiao et al. 2003). This less restrictive cutoff level of FPG brought about a decrease in the proportion of people with IFG combined with IGT, but it increased the proportion of IGT combined with IFG (WHO 2006). In the Atherosclerosis Risk in Communities (ARIC) Study, isolated IFG was more common in men and black women. Persons with isolated IFG were statistically younger, current smokers, and alcohol consumers than those with IGT. They also had a higher BMI, waist circumference, increased fasting insulin level, higher LDL cholesterol, and a lower content of HDL cholesterol. In contrast,

higher triglyceride content, systolic blood pressure, and leukocyte count were more commonly noticed in persons with isolated IGT (Pankow et al. 2007).

5 Course and Adverse Outcomes

As subjects with IFG are a heterogeneous group, frequently with other concomitant disorders of glucose metabolism, the risk of progression to diabetes widely varies. Nonetheless, IFG should be seen as a risk factor for diabetes and adverse outcomes (WHO 2006). The development of diabetes and its complications is a gradual and complex process. The blood glucose level gradually increases over time until it exceeds the diagnostic criteria for diabetes (Færch et al. 2013). The progression of IFG to diabetes is not a must. A significant proportion of people revert to normoglycemia, or the process halts at the prediabetic stage (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018). Approximately, a third of the subjects with IFG will develop diabetes within 5–7 years (Unwin et al. 2002). Many factors, inter alia, nonuniform inclusion criteria in various studies, different definitions, different diagnostic tests for confirmation of IFG and diabetes, and a wide range of observation and follow-up periods result in significant differences in the findings. For instance, data from the Hoorn Study indicate that 33% of the people with isolated IFG and 64.5% with both IFG and IGT develop diabetes during a mean follow-up of 6.4 years, in comparison with 4.5% of those with normal glucose regulation at baseline. The survey was conducted among nondiabetic Caucasian residents of Hoorn in the Netherlands, aged 50–75 years, from 1989 to 1998 (de Vegt et al. 1998, 2001). An Italian study conducted among telephone company employees aged 40–59 years reported a much lower number of people with isolated IFG and with combined IFG and IGT who progressed to full-fledged type 2 diabetes. The proportion was just 9.1% and 44.4% after 11.5 years of the follow-up period, respectively. That study, however, raises methodological misgivings as there was only one person with isolated IFG and nine persons with both IFG and IGT. The odds ratios were 10.3 (95% confidence interval (CI) 2.2–46.8) and 1.2 (95% CI 0.3–10.2), respectively (Nichols et al. 2007; Vaccaro et al. 1999).

In the multiethnic Mauritius population, where the incidence of diabetes is high, the findings in people, aged 25–79, with IFG observed for 11 years were as follows: 38% (95% CI 28.5–47.5) reverted to normoglycemia, 7% (95% CI 2.0–12.0) retained IFG, 17% (95% CI 9.6–24.4) developed IGT, and 38% (95% CI 28.5–47.5) progressed to diabetes (Soderberg et al. 2004). In a study among Pima Indians, who have the highest prevalence of type 2 diabetes in the world, the risk of progression of prediabetes to diabetes is considerably higher in IFG than that in IGT. The 5-year cumulative incidence of type 2 diabetes in people with normal glucose regulation, isolated IGT, isolated IFG, and IFG/IGT combined was 3.6%, 19.9%, 31.0%, and 41.2%, respectively (Gabir et al. 2000b). In a Hong Kong study, 30.9% (n = 17) persons with IFG reverted to normoglycemia, 43.6% (n = 24) sustained the IFG status, and 25.5% (n = 14) progressed to diabetes after a median follow-up period of 1.12 years. It should be underlined that this study group was small (n = 55) and young (mean age 37.4 ± 9.3 years) but had a high risk of diabetes, including a family history of diabetes or gestational diabetes, overweight, and hypertension. Also, the period of observation was rather short (Ko et al. 2001).

In the Toranomon Hospital Health Management Center Study 3 (TOPICS 3), conducted in 6,241 Japanese participants, aged 24–82, without diabetes at baseline, prediabetes was newly diagnosed in 1,682 subjects. The prediabetic subjects were divided into three groups: 1/ isolated IFG (HbA1c <5.7% and FPG 5.6–6.9 mmol/L), 2/ isolated elevated HbA1c (HbA1c 5.7–6.4% and FPG <5.6 mmol/L), and 3/both HbA1c 5.7–6.4% and FPG 5.6–6.9 mmol/L. The groups consisted of 20.3% (n = 1,270), 6.6% (n = 412), and 6.6% (n = 410) subjects, respectively. Over the mean 4.7 year-long follow-up, diabetes (FPG >7.0 mmol/L, HbA1c >6.5%)

was diagnosed in 6.4% (n = 108), 1.8% (n = 30), and 9.2% (n = 154) of the subjects, respectively (Wilson 2017). According to the Toranomon Hospital Health Management Center Study 4 (T OPICS 4), conducted in a similar cohort with a 5-year follow-up, normoglycemia (neither HbA1c nor FPG elevated) was achieved by 20.5–32.0% of the participants diagnosed as having prediabetes at baseline, based on any one of the four criteria FPG 5.6–6.9 mmol/L, FPG 6.1–6.9 mmol/L, HbA1c 5.7–6.4%, or HbA1c 6.0–6.4% (Heianza et al. 2012).

A meta-analysis of multiple cohort studies shows the absolute annualized risk of progression of impaired glucose metabolism to full-fledged diabetes of 5–10%. The relative risk was 4.66 (95% CI 2.47–6.85) for IFG and 7.54 (95% CI 4.63–10.45) for isolated IFG. For comparison, in subjects with IGT and isolated IGT, the risk ratio was 6.35 (95% CI 4.87–7.82) and 5.52 (95% CI 3.13–7.91), respectively. The highest relative risk was 12.13 (95% CI 4.27–20.00) in a population with both IFG and IGT (Gerstein et al. 2007). These studies show that people with IFG and coexisting other glycemic disorders (IGT, elevated HbA1c, etc.) have a substantially increased risk of developing diabetes. Some authors indicate that all subjects with both FPG 6.1–6.9 mmol/L and HbA1c 6.0–6.4% develop diabetes over 5 years (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018; Heianza et al. 2012). Divergent results concerning the rate at which diabetes mellitus would like to develop stem from the unknown duration of impaired glucose regulations. The only study that traced the development of type 2 diabetes from the onset of abnormal glucose regulation is the Baltimore Longitudinal Study of Aging (Nichols et al. 2007). Of 488 participants with normal glucose regulation, aged 20–89 years, 14% progressed to IFG and 48% developed IGT after 10 years. In the same period, 8% of the participants with IFG and 27% with IGT developed diabetes. The lowest progression rate to diabetes is in the persons with an isolated elevation of FPG (Meigs et al. 2003).

The ADDITION-Denmark study reported that the overall incidence of diabetes is 3.51 (95% CI 3.32–3.72) *per* 1,000 person-years. In comparison with a low-risk reference group, the incidence in persons with prediabetes was significantly higher, amounting to 14.61 (95% CI 11.28–18.92), 21.83 (17.08–27.89), and 40.81 (95% CI 32.19–51.74) for isolated IFG, isolated IGT, and combined IFG and IGT, respectively. The pattern profile of the incidence of diabetes over a 10-year-long follow-up also was different. For the groups of persons with impaired glucose regulation outlined above, the incidence rate peaked during the first 2 years after the baseline tests, whereas it remained at a constant level during the first 6 years in the low-risk persons (Rasmussen et al. 2016).

As discussed above, the progression from prediabetes to diabetes depends on the spate of risk factors. The most frequently mentioned are the following: age; genetic factors including race and ethnicity, family history of diabetes, gestational diabetes, obesity (particularly central obesity), dyslipidemia, hypertension, high FPG, and plasma insulin levels; poor β-cell function; smoking; and sedentary lifestyle (Fonseca 2009; Levitzky et al. 2008). Stratton et al. (2000) reported that the higher the average blood glucose level, the greater is the risk of progression to diabetes and its micro- and macrovascular complications. The American College of Endocrinology and the American Association of Clinical Endocrinologists suggest that the diagnosis of metabolic syndrome is equivalent to a prediabetic state (Garber et al. 2008). Additionally, there are novel risk factors that are conducive to the development of diabetes such environmental contaminants, depression, vitamin D and K deficiency, and iron overload (Wolf et al. 2019; Chatterjee et al. 2015; Wu et al. 2014; Chan et al. 2009). Toshihiro et al. (2008) have also described the potential influence of psychosocial risk factors such as night work shifts, daily life stress, and holding a high administrative post, whereas being a nonsmoker, having a white-collar job, and a low serum alanine aminotransferase (ALT) are mentioned as possible protective factors against the development of diabetes. Nonetheless, there is limited and rather inconsistent knowledge of the factors influencing the

transition from isolated IFG to full-fledged diabetes (Meigs et al. 2003).

Most pro-diabetic factors are also associated with risk for cardiovascular diseases (CVD). Thus, people with prediabetes could benefit from cardiovascular risk factor modifications (Yeboah et al. 2011). Conversely, the risk of isolated IFG for fatal and nonfatal cardiovascular events also is considered. Isolated IGT might be a particularly strong contributor to CVD (Pankow et al. 2007; DECODE Study Group 2003; Unwin et al. 2002). Persons with combined IFG and IGT are at risk of worse cardiovascular outcomes (Diabetes Canada Clinical Practice Guidelines Expert Committee et al. 2018; Buysschaert et al. 2016). Studies indicate that the overlap of IFG and CVD risks decreases when the new IFG definition by ADA is employed (Abraham and Fox 2013; Soulimane et al. 2012; WHO 2006). Current guidelines for the prevention of type 2 diabetes recommend lifestyle interventions as fundamental management. Patients diagnosed with dysglycemia should be counseled to achieve and maintain a 7% body weight reduction and to enhance moderate-intensity physical activity to at least 150 min *per* week (American Diabetes Association 2020). Disappointingly, most people with prediabetes are undiagnosed and untreated. Statistics are alarming. According to the National Health and Nutrition Examination Survey (NHANES) performed in the US adult population in 2005/2006, solely 3.4% of persons with IFG and/or IGT reported that their physicians diagnosed them as being at the prediabetic stage. Only was a third of them counseled on physical activity and diet. Of those who reported performing physical exercise, only did half fulfill the then ADA recommendations to this end (Karve and Hayward 2010).

There is strong evidence that lifestyle modifications are effective in people with IGT. Most studies have been performed in persons with isolated IGT or combined IFG and IGT, such as the Finnish Diabetes Prevention Study (Toumilehto et al. 2013), the Diabetes Prevention Program Outcomes Study (Knowler et al. 2009), the Indian Diabetes Prevention Program (Ramachandran et al. 2006), the Diabetes Prevention Program Research Group (Knowler et al. 2002), and the Da Qing IGT and Diabetes Study (Pan et al. 1997). It remains unclear whether a similar effect is attainable in a group with isolated IFG (Huang et al. 2016; Rasmussen et al. 2016; Saito et al. 2011). Studies primarily focus on weight loss and increasing physical activity. There is a need to better understand how food and diet influence β-cell function and insulin sensitivity (Guess 2018). Preventive pharmacotherapy should be considered in people with dysglycemia, particularly in those with obesity, under 60 years of age, and in women with a history of gestational diabetes (ADA 2020). Out of the several drugs that could prevent or delay the onset of diabetes, such as metformin (Knowler et al. 2009; Knowler et al. 2002), glucagon-like peptide-1 receptor agonist (Kim et al. 2013), thiazolidinedione (DeFronzo et al. 2013; Hanley et al. 2010; DREAM et al. 2006), α-glucosidase inhibitors (Chiasson et al. 2002), or orlistat (Torgerson et al. 2004), only has metformin been approved for diabetes prevention (American Diabetes Association 2020).

6 Conclusions

In conclusion, the progression of impaired fasting glucose to full-fledged diabetes mellitus is not inevitable. Impaired fasting glucose and impaired glucose tolerance differ in the prevalence, underlying pathophysiology, risk of conversion to diabetes, mortality, and cardiovascular outcomes. Risks are substantially higher when impaired fasting glucose coincides with impaired glucose tolerance. Further studies are needed for a better understanding of how to delay or prevent the progression of isolated impaired fasting glucose to diabetes, regarding lifestyle, dietary, and pharmacological interventions. Individually tailored interventions based on the underlying pathophysiology should be performed in the optimal management program for diabetes prevention in patients with impaired glucose regulation.

Conflicts of Interest The authors declare no conflict of interest concerning this article.

Ethical Approval This review article does not contain any studies with human participants or animals directly performed by any of the authors.

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Oleosins: A Short Allergy Review

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Abstract

In patients having a history of anaphylaxis after consumption of peanuts, sunflower seeds, or soy and skin or blood tests negative for the allergen extracts, oleosins could be the culprit. Oleosins are common and largely underestimated allergy inducers of plant origin, causing severe allergy symptoms, including the anaphylactic shock. They are resistant to high temperatures and digestive enzymes. The consumption of heat-treated oleosins has been associated with a higher risk of a severe anaphylactic reaction. Recent studies have shown that oleosins could be a biomarker of the allergy severity to peanuts. Oleosins have a hydrophobic structure and thus, are poorly soluble in aqueous solutions. The aqueous extraction, separation, and purification procedures do not guarantee their solubility. Oleosins dissolve only in the presence of detergents, which limits their use in both in vivo and in vitro allergy tests. Recently, a multiparameter allergy test that detects the allergen-specific immunoglobulin E (sIgE) against oleosins has become available. This capability may help to unravel the presence of oleosin source during the routine diagnostic of allergy, which is conducive to assessing the risk for severe anaphylaxis and may also help to clarify the ambiguous allergy cases.

Keywords

Allergy · Anaphylaxis · Biomaker · Diagnostic tests · Oleosin · sIgE

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1 Introduction

The consumption of peanuts, one of the most common allergen, may cause a severe anaphylactic reaction (Kleine-Tebbe and Jakob 2017). Allergy symptoms can be provoked by a minute quantity of peanuts (Blom et al. 2013). The early diagnosis of peanut allergy may prevent a severe anaphylactic reaction. Astonishingly, in some patients with symptoms and history of allergy to peanuts or other seeds like sesame and hazelnut, the skin prick test (SPT) and the identification of

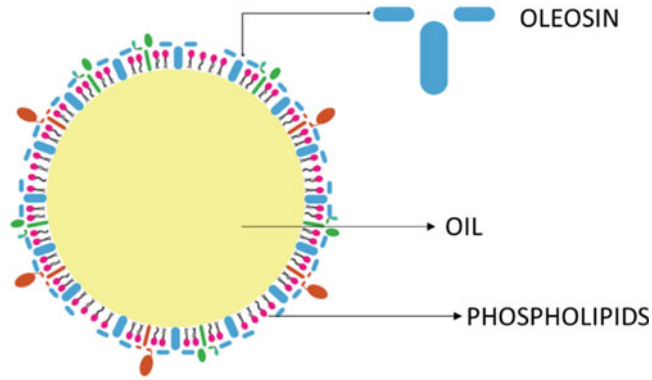

Fig. 1 A scheme of an oleosome, oil droplet. Oleosins are the key proteins present in the membrane of an oil body

specific immunoglobulins E (sIgE) against allergen extracts may not firmly establish the sensitization (Ehlers et al. 2019; Schwager et al. 2017). Double-blind placebo-controlled food challenges are necessary in such cases. This type of examination is expensive and potentially dangerous for the patient, as it may result in anaphylactic shock. Recent advances in the molecular diagnostics, based on the in vitro detection of a serum sIgE level against allergen molecules, offer a way to resolve such difficult cases. That also includes allergy to traces of peanuts and other seeds in ingested food where the oleosin family of molecules might be responsible for the unexplained allergy symptoms.

Oleosins are plant-derived proteins with the molecular weight ranging from 15 kDa to 24 kDa. These protein molecules are constituents of oil bodies known as oleosomes that store triglycerides as an energy source during the germination process of seeds like peanuts, hazelnuts, walnuts, almonds, soybeans, sesame and rapeseeds (Zuidmeer-Jongejan et al. 2014). The central part of the oleosome consists of a hydrophobic domain referred to as a core, built of 72 amino acids, the longest known hydrophobic domain. The N-terminal domains, present on the outer ring, are either hydrophilic or amphipathic, whereas the C-terminal domain is always amphipathic. Oleosins, due to a unique structure, stabilize the oleosomes, preventing them from coalescence (Fig. 1). Oleosins are common energy storage proteins in plants. The first identified oleosin has been a peanut protein (Pons et al. 2002). Since then a few more peanut oleosin allergens have been discovered, such as Ara h 10, Ara h 11, Ara h 14, and Ara h 15. The hazelnut oleosin allergens are Cor a 12, Cor a 13, and Cor a 14. The sesame seeds contain the molecules Ses i 4 and Ses i 5, belonging to the oleosin family (Jappe et al. 2019). The general characteristics of oleosins are presented in Table 1.

The hydrophobic nature of oleosins makes them hardly soluble in aqueous solutions (Ehlers et al. 2017; Schwager et al. 2017). Therefore, the use of oleosins in both in vivo and in vitro allergen testing is limited, unless a detergent is added to the system (Scala et al. 2018). An important feature of oleosins is the resistance to heat and digestion. There is a biological plausibly that stability of the oleosins' structure is conducive to their high potential of evoking allergy symptoms, including anaphylactic shock (Kleine-Tebbe and Jakob 2017).

2 Clinical Implications

Schwager et al. (2017) have investigated the capacity of sIgE to bind with Ara h 10/11 and Ara h 14/15 in the serum of patients who experienced a severe anaphylactic reaction after eating peanuts. The authors found that sIgE was tightly attached to the molecules from roasted but not raw peanuts. The control group was formed by patients who were sensitized to peanuts but tolerated them and patients who were not

Table 1 Summary of oleosins' features in nuts and seed, the proteins of 15–24 kDa accumulating on the surfaces of oil bodies

Peanut: Ara h 10, Ara h 11, Ara h14, and Ara h 15
Hazelnut: Cor a 12, Cor a 13, and Cor a 14
Sesame: Ses i 4 and Ses i 5
Highly resistant to heat and digestion
Hydrophobic
Lipid soluble, which make them elude common extraction, separation, and purification procedures
Patients sensitized to oleosins from one kind of seeds are likely to be cross-sensitized to oleosins from other sources, which is explicable by the presence of the identical amino acid sequence in C-terminal
Induction of sIgE in the blood is responsible for allergy symptoms after consumption of oleosin-containing food
Food processing at high temperature, e.g., roasting, is associated with a higher risk of allergic symptoms
Introduction of the detection of sIgE against oleosins into the routine diagnostic tests would facilitate the risk assessment for anaphylaxis and help explain unequivocal symptomatic cases linked to consumption of seed-containing food
Oleosins are a candidate biomarker of allergic symptom severity to peanuts; the most widely consumed nuts

sensitized to peanuts. In both groups, serum sIgE failed to bind either to molecules derived from raw or roasted peanuts. Then, the basophil activation test was performed with peanut molecules that belong to the oleosin family. In the test, higher reactivity was noticed when oleosins from roasted peanuts were used, which was particularly evident in patients with a history of severe allergic symptoms. The explanation of these findings might be that the process of roasting deprives oleosins of a protective effect of lipids, which delays the peanut digestion (Kleine-Tebbe and Jakob 2017). Consequently, the consumption of oleosins that underwent thermal processing may increase the risk of severe anaphylaxis. Studies performed with sesame seeds and hazelnuts have also confirmed that consumption of thermally processed seeds facilitates the development of allergy symptoms (Zuidmeer-Jongejan et al. 2014; Leduc et al. 2006). Therefore, there appears a consistent impression that the most relevant explanation of severe anaphylactic reaction in peanut allergy is the presence of sIgE against oleosins in the serum (Schwager et al. 2017; Ballmer-Weber et al. 2015).

The risk assessment of severe anaphylaxis in peanut allergy seems essential since this kind of allergy is widespread. Every fourth patient sensitized to peanuts has sIgE against oleosins in the serum. Moreover, sensitization to oleosins is more common among children than among adults (Datema et al. 2015). Therefore, the introduction of oleosins into the routine diagnostic tests would significantly improve the diagnostics and would help tailor the therapeutic recommendations to the sensitization profile of a patient. The only one test allowing the detection of sIgE against oleosins is a third-generation multiparameter ALEX2® that reveals if the patient is sensitized to the peanut oleosin Ara h 15.

Regarding peanut allergy, another important aspect concerning the molecules Ara h 8 (a representative of PR-10 group) and Ara h 9 (belonging to nsLTP) should be mentioned. In a raw peanut, these molecules are affiliated with lipids that protect the proteins from enzyme-mediated digestion in the intestinal tract (Jappe et al. 2019). A connection between Ara h 8 and lipids explains why mono-sensitization against this molecule is responsible for peanut tolerance or mild allergic symptoms. There is evidence that roasting and long-term storage of peanuts causes oxidation of the protective lipids attached to Ara h 8, which leads to structural changes in the molecule or the formation of other compounds. Hence, resistance to heat and digestion resistance of the molecule is reduced and sIgE against Ara h 8 becomes more reactive (Bublin et al. 2014). Enhanced sIgE binding to antigens after roasting has also been noticed for other peanut molecules such as Ara h 9, Ara h 12, and Ara h 13. The last two of these molecules belong to the family of defensins (Jappe et al. 2019).

3 Cross-Reactions with Oleosins of Different Origin

As revealed in a study involving 423 patients, who lived in the European cities and were sensitized to hazelnuts, sensitization to oleosins is a common occurrence, ranging from 10% to 25% of the population (Datema et al. 2015). Referring to the cross-reactivity, the authors observe that sensitization to Cor a 12, a hazelnut oleosin, correlates with sensitization to fat-rich sesame and sunflower seeds. There also is cross-sensitivity to pollen from various plants and latex. In light of this report, the question arises of whether sensitization to pollen oleosins can result in IgE-mediated reactions caused by oleosins from seeds. Genetic analysis of oleosins might give a deeper insight into this issue. It has been shown that pollen oleosins evolved from seeds oleosins, but their N-terminal domain is shorter while the C-terminal domain is more built out. It means that there is little similarity between pollen and seed oleosins, except for the hydrophobic core. Since the core is thought to be non-antigenic, cross-reactivity between pollen and seed oleosins is rather unlikely to happen (Jappe and Schwager 2017).

Schwager et al. (2017) have formed a different hypothesis to explain cross-reactions in patients sensitized to oleosins, based on the analysis of a structure of rAra h 15 molecules in peanuts. The authors show that an amino acid sequence in the C-terminal domain of this molecule displays the highest IgE-binding affinity. It appears that the same sequence is present in oleosins from other seeds such as hazelnut, rapeseed, soybeans, sesame, and almond. Therefore, cross-reactions with oleosins from various seeds are more likely to happen in the serum of patients who are sensitized to oleosins from a seed source. Paraphrasing, patients who are sensitized to oleosins from a specific seed are more likely to have allergy symptoms after eating other seeds due to cross-reactions.

Jappe and Schwager (2017) have failed to show the association between sensitization to seed oleosins and pollen, investigating 74 peanut-allergic patients from northern Germany. However, the authors suggested that oleosins could be regarded as a marker of symptoms severity in peanut allergy. They also found that 52 out of the 53 patients, who experienced an anaphylactic reaction after the consumption of peanuts, had sIgE against oleosins in the blood. The remaining 21 sensitized patients had neither appreciable symptoms related to peanut consumption nor sIgE against oleosins. Sensitization could result from the cross-reaction of immunoglobulins against other peanut and pollen allergen molecules. Pollen is rather doubtful as the oleosin-sensitized patients experienced first symptoms of genuine peanut allergy in childhood, which was unaccompanied by pollen allergy at the time. The lack of sIgE against peanut oleosins in the sensitized patients also puts into question the cross-reactivity with oleosins originating from other seeds. However, other possibilities remain as oleosins show sensitization pattern akin to profilins and cross-reactive carbohydrate determinants (Datema et al. 2015).

4 Benefits from Introducing Oleosins into Routine Allergy Diagnostic Tests

The development of new methods of extraction of allergen molecules extends the understanding of the mechanisms of allergic reactions. There appears a consensus that oleosins underlie the allergy to peanuts and other seeds. Therefore, these molecules should be included in routine diagnostic tests, with benefits to patients, as peanuts are considered wholesome and their consumption is ubiquitous. Peanuts are also the most common sensitizing allergens, often provoking dire health effects in the form of anaphylactic shock. The detection of sIgE against oleosins could help assess the risk of anaphylaxis. Moreover, the molecular diagnostics of sensitization against oleosins would enable the avoidance of troublesome and potentially dangerous food challenges in patients with a history of anaphylactic reaction after the contact with seeds and in

those with unequivocal results of skin prick test or sIgE against allergen extracts in vitro.

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Shortage of Physicians: A Critical Review

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Abstract

A recent report of the Organization for Economic Co-operation and Development (OECD) points out an insufficient number of physicians in Europe. The issue seems especially relevant in the face of the COVID-19 pandemic. In this review, based on papers found in the PubMed database, we drew on the available information on the aspects of medical education and terms and rate of employment of physicians to submit potential solutions of how to increase the availability of physicians in Europe. We offer the following improvements in tackling the issue: (i) standardization of the method of verification of the number of physicians in practice for a meaningful comparison between European states; (ii) managerial reorganization of medical education to increase the flexibility of teaching; (iii) education shortening, e.g., to 4 years, for nurses, paramedics, and the like; (iv) circumscription of unnecessary health records and the use of artificial intelligence to streamline the recording system to ease the burden on the medical staff.

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Keywords

Hospital management · Medical policy · Medical study · Shortage of physicians

1 Introduction

One of the biggest challenges of modern Europe is its aging population, which in upcoming decades will introduce a heavy burden on healthcare systems and economies. European states have achieved spectacular success in prolonging human life, with the average lifespan going currently beyond 80 years of age. Simultaneously, the total fertility rate, i.e., the average number of children born to a woman over her lifetime, has declined below the standard generational replacement level of 2.1. In Germany, this rate oscillates around 1.6 and, with 28% of the population being over 60, it faces a catastrophe that requires to add the fifth level to the demographic development model. In the aging society, providing enough physicians and nurses has become a primary concern. A recent report of the Organization for Economic Co-operation and Development (OECD) points to an insufficient and declining number of physicians in Europe. That seems especially relevant in the light of the recent COVID-19 pandemic (Barcelona Field Studies Center 2020; Macrotrends 2020; UN 2020; Eurostat Statistics Explained 2019). Therefore, we set out in this

review to critically address the challenges related to a shortage of physicians and suggest possible solutions that could enhance the availability of physicians in Europe. The review is based on the articles concerning the physician shortage in Europe appearing in the PubMed database as of June 18, 2020. The search was conducted using the term "physician shortage", which returned 4328 publications. The OECD statistics concerning healthcare resources and health status in European countries were also considered.

2 European Countries Facing a Shortage of Physicians

An overwhelming majority of publications state that there is a serious shortage of physicians in Europe and that it is going to increase with time. However, the discussion should begin with a careful analysis of how the total number of physicians is estimated. The real problem might lie in the uneven distribution of medical personnel in particular countries and areas. Discrepancies are especially visible when it comes to urban and rural areas. It is also imperative to consider the aging of the physician population (WHO 2020; European Data Journalism Network 2018). In 2012, the European Commission forecast a possible two million shortage of medical personnel, a vague statement itself. In 2018, the main highlighted problems were a shortage of general practitioners despite the increasing number of doctors per capita in the EU, and the expected decline in the availability of healthcare in rural areas (OECD 2018; European Commission 2012).

The first problem is a variety of ways in which the total number of physicians is calculated in different countries. In Greece, which supposedly has the largest numbers of doctors per capita standing at 6.3 doctors *per* 1000 population, or Portugal at 4.4 doctors *per* 1000 population, data include all the licensed physicians, also those who moved abroad. This way of assessment strongly contrasts the OECD's definition of "practicing physician". Thus, analysts assume that the overestimation in Portugal could be as big as 1/3 of the officially provided value. In the case of Slovakia with 3.4 doctors *per* 1000 population, the Netherlands with 3.4 *per* 1000 population, and France with 3.3 *per* 1000 population, the official data incorporate not only the physicians directly taking care of patients, but also those working as university scholars, researchers, and even managers, which increases the statistics by 5–10%. The over- or underestimation of the actual number of physicians in the EU is a significant hindrance to the true problem assessment (OECD 2020).

The EU Commission assessment of the number of physicians is based on OECD's statistical forecasts. Therefore, a universal definition of "practicing physician" would render the cross-countries assessment more precise and reliable. For instance, doctors who analyze in silico orthopedic implants are not considered practicing physicians, as they have no direct contact with patients. On the other hand, doctors working abroad are usually included in the overall number of physicians in the country that they had left and all too often in the country of current abode and work.

While analyzing the statistics, it is impossible to overlook the problem of a "brain drain" in Europe. Despite the increasing number of physicians, a 5% growth between 2010 and 2020, compared to an average 3% growth in other occupational groups, uneven distribution of medical school graduates presents a challenge to the current system. Staggering differences in the remuneration of doctors inside the EU, from several hundred euro a month in Estonia or Romania to 4000 or more euro in western and northern Europe, promote an exodus of young physicians from East to West and South to North. Estonia had 4312 practicing physicians in 2004, since then over 1800 of them have applied for the recognition of qualifications abroad. Considering that most of the migrating doctors are young people, another problem becomes intensified, notable the aging of doctors' population, let alone the population at large (Berthier 2018; Hervey 2017).

There are other factors worth considering. The European Commission's report shows that an average doctor sees 2147 patients every year –

679 in Sweden, 3457 in Hungary, and 3311 in Slovakia. It would be worthy of narrowing these statistics down, looking at regional distribution in a country, targeting the overwhelmed general practices, and establishing how many physicians are needed in a particular place. A low density of physicians in rural areas, i.e., with the population below 150 people *per* kilometer squared, is one of the leading problems pointed out by the European Commission. The situation is especially alarming in Finland, Germany, Czechia, France, and Slovakia. Encouraging young physicians to work in rural areas, particularly in places where they have no personal ties, is an issue throughout Europe. Some of the methods implemented to battle this problem include financial help in funding general practices and promoting applications to medical schools from students with a rural background. An interesting example is a shortened 4-year-long graduate medicine program offered by the University of Dundee in Scotland, whose aim is to enthuse potential general practitioners about working in rural areas (OECD 2018, 2020; University of St. Andrews 2020; Wilhelmi et al. 2018; European Commission 2012).

The next question that needs to be addressed is the age of practicing physicians. In 2009, around 30% of all European doctors were 55 years old or above, which is a consistent trend associated with the "baby boom" generation reaching the retirement age. An estimated percentage of physicians older than 55 years old in Europe has risen from 28% in 2007 to 38% in 2017. The countries where healthcare systems are especially jeopardized by this tendency include Germany, France, and Italy where doctors within this age group make up almost half of the entire occupational group. In comparison, the UK only has 14% of physicians above the age of 55, which might be caused by the fact that almost 25% of the country's doctors come from abroad, and young physicians from all over Europe are prone to seek employment in the UK (Eurostat Statistics Explained 2019; Triggle 2016).

There is a different side of the problem. It can be argued that older physicians with longer professional experience will be sought-after in the aging society, as seniors might feel more comfortable to confide in them rather than in young graduates. At the same time, it is crucial to remember that the role of general practitioners is fundamentally different from the one of neurosurgeons who perform intricate procedures requiring immaculate dexterity. A solution for the uneven distribution of physicians between rural and urban areas could be to encourage older doctors to move to the countryside, especially when they are reluctant to continue their careers in demanding clinical specialties due to cognitive and physical decline. Research conducted by McMaster University in the city of Hamilton in Ontario, Canada, as part of the Physician Review and Enhancement Program (PREP) shows that along with physician's increasing age, the chances of involuntary oversight of patients' needs are significantly rising. Some of the negative outcomes where more advanced age plays a role include non-comprehensive history taking, incomplete data gathering, and leaving out details in patient records. However, the same study also shows that older physicians perform better at accurate diagnosing (Eva 2002).

3 Specialization Trends Among Doctors in the Light of Shortages

Other notable issues are shortages in particular specializations and general practitioners despite the rising number of physicians. Most European doctors are specialists, their ratio to general practitioners is 3.2 to 1.0, nearly 12 to 1 in Greece, a trend that has remained unchanged for a decade, but some specialty gaps are yet unfilled. For instance, France faces shortages of obstetricians and gynecologists, while Bulgaria or Spain deal with an insufficient number of anesthesiologists or psychiatrists (WHO 2020; Eurostat Statistics Explained 2019; European Commission 2012). The analysis of graduates' choices regarding their potential specialization is a complex problem. In the UK, the National Health Service regularly evaluates the specialization trends among young doctors. According to

the 2016 study, 27.8% of the interviewed graduates declared their first choice to be general practice, followed by anesthesiology (12.1%), pediatrics (8.6%), general medicine (8.5%), and emergency medicine (5.6%). However, further years have shown decreasing interest in choosing a general practice, and a rise of interest in anesthesiology, radiology, and psychiatry (Wilhelmi et al. 2018).

A simple glance at data does not show the full scope of the problem. A report by the National Health Service emphasizes that the percentage of graduates planning to pursue a career in general practice makes up less than half of the UK's demand. Voices can be heard about dramatic shortages in the radiology sector, with as much as one-third of all radiologists in the UK being foreigners. Special recruitment actions have been organized to increase interest, with limited success. The Royal College of Radiologists highlights that the uncertainty caused by Brexit, with the expected difficulties of acquiring visas and transferring families to the UK, may have an impact on the foreign physician's willingness to fill up the openings. Currently, almost 99% of the UK's radiology departments cannot meet imaging and X-ray demands (European Union of Medical Specialists 2019; Lambert et al. 2018; Lambert and Goldacre 2011).

4 Methods of Widening Access to Medical Studies

Widening access to medical studies might yet be the most reliable way to prevent the physician shortage. Currently, there are several ways of getting a medical license in Europe. The most common in continental Europe is enrolling in a 6-year-long program of medical courses. This is an MD program with no specialization. There are three study cycles in France, two of which – PCEM and DCEM (Première/Deuxième Cycle des Études Médicales) – collectively last 6 years, with the third one focusing on specialization. A similar approach is popular among medical schools in Germany, Finland, Italy, and Poland. The UK offers a 5-year-long bachelor's program in medicine leading to the degree of Bachelor of Medicine, Bachelor of Surgery (MBBS), after which graduates receive a temporary license. The next step is the Foundation Program, lasting 1–2 years, allowing to apply to the General Medical Council (GMC) for a permanent license. An alternative option is receiving a 4-year-long postgraduate diploma in Graduate Entry Medicine. Its equivalent in continental Europe is offered by some countries, like Poland and Czechia, but created mostly to attract foreign students, and requiring tuition fees while the regular 6-year-long program is free in these countries (Balan 2020; Killingbeck 2013).

The last model shows a lot of potential in terms of reducing the physician shortage in Europe. Although often criticized, for instance, the Portugal Medical Association describes it as being of doubtful quality and unnecessary, it widens access to medical studies. It can be argued that the 6-year-long study often does not seem like the right career choice for high school graduates. The choice may also be hampered by the entry exams obligatory in many European countries, which makes it difficult to gain real-life experience in the healthcare environment before applying. Deciding to pursue a physician's education path might seem overwhelming at a young age. Instead, high school graduates often settle for Biological or Medical Sciences. It is a reasonable assumption that a degree in a related discipline could be a sufficient foundation for an accelerated program in medicine. Thus, creating the possibility of an accelerated tuition-free 4-year-long medical study, taught in English in most European medical schools, would be a step toward mitigating a downtrend in the number of physicians (Martinho 2012). The implementation of this idea might lead to more students graduating with a medical degree. Moreover, the knowledge and skills of biologists or biomedical scientists, whose job prospects in some of the European countries are off-putting, would greatly supplement their medical training, allowing the society to benefit from extensively educated graduates.

5 New Technologies in Aid of Limiting a Shortage of Physicians

The volume of health records grows every year. A study carried out in 2016 shows that doctors use 27% of their work time directly interacting with their patients, compared to 49% of the time spent on filling in health records. Solving this problem requires an in-depth verification of the currently existing system of the accumulation of health records and erasure of the duplicated or redundant elements. Improvements in the electronic health system could limit the load of documentation, and by doing so, increase the amount of time available for spending with the patient. Extensive research has been conducted showing that modern technologies, like artificial intelligence (AI), can limit the post-surgery complications, so much as by one-third, significantly decreasing direct and indirect costs of treating patients, but also saving the medical personnel's time. The AI is already utilized in the healthcare field as a useful tool for scheduling appointments, online check-ins, or reminder texts for check-ups. There have been cases where AI systems outperformed experienced physicians in diagnosing diseases, especially when basing on visual data, such as classifying skin deformations or tuberculosis on chest radiographs. Although even the most advanced technologies cannot completely replace physicians in the nearest future, benefiting from its time-saving abilities could improve the efficiency of European healthcare systems (Amisha et al. 2019; Vinanzi et al. 2019; Jiang et al. 2017; Lorkowski and Wilk 2017).

6 Conclusions

The physician shortage Europe faces right now appears a complex and somewhat paradoxical issue, considering the growing numbers of medical graduates. Solutions proposed in this article could help increase the number of physicians in the sought-after specializations and rural areas. Suggested solutions are as follows:

- International standardization of the method of estimating the number of practicing physicians.
- The shortage of physicians in Europe, both general practitioners and specialists, should be verified using the counting methods presented by the European Organization for Economic Co-operation and Development (OECD).
- Key issues are the aging of the physician population and an inflexible organization of medical schools.
- It could be beneficial to introduce medical studies of shorter duration, for instance, 4 years long, for nurses, paramedics, and biological/medical science graduates in European countries.
- A circumscription of the overload of medical records using the artificial intelligence-based methods would enable physicians to devote more time to patients, the mission they are charged with.

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Fluid Therapy in Patients Undergoing Abdominal Surgery: A Bumpy Road Towards Individualized Management

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Abstract

Prudent intraoperative fluid replacement therapy, inotropes, and vasoactive drugs should be guided by adequate hemodynamic monitoring. The study aimed to evaluate the single-centre practice on intraoperative fluid therapy in abdominal surgery (AS). The evaluation, based on a review of medical files, included 235 patients (103 men), aged 60 ± 15 years who underwent AS between September and November 2017. Fluid therapy was analyzed in terms of quality and quantity. There were 124 high-risk patients according to the American Society of Anaesthesiologists Classification (ASA Class 3+) and 89 high-risk procedures performed. The median duration of procedures was 175 (IQR 106–284) min. Eleven patients died post-operatively. The median fluids volume was 10.4 mL/kg/h of anaesthesia, including 9.1 mL/kg/h of crystalloids and 2.7 mL/kg/h of synthetic colloids. Patients undergoing longer than the median procedures received significantly fewer fluids than those who underwent shorter procedures. The volume of fluids in the longer procedures depended on the procedural risk classification and was significantly greater in high-risk patients undergoing high-risk surgery. Patients who died received significantly more fluids than survivors. In all patients, a non-invasive blood pressure monitoring was used and only six patients had therapy guided by metabolic equilibrium. The fluid therapy used was liberal but complied with the recommendations regarding the type of fluid and risk-adjusted dosing. Hemodynamic monitoring was suboptimal and requires modifications. In conclusion, the optimization of intraoperative fluid therapy requires a balanced and standardized approach consistent with treatment procedures.

Keywords

Abdominal surgery · Fluid replacement therapy · Hemodynamic monitoring · Intraoperative condition · Surgical risk

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1 Introduction

More than 300 million surgical procedures are performed worldwide every year, and the number is constantly growing due to increasing clinical needs, ageing population, and the development of surgical techniques (WHO 2020; Rose et al. 2015). Patients undergoing major surgery are at high risk of increased postoperative morbidity and mortality. The practice regarding fluid balance is crucial for the safe and effective intraoperative management of patients. The definition of the optimal intravenous fluid dose is still undetermined. The physician's approach to intraoperative fluid therapy is customarily described as liberal or restrictive. However, the insurance of hemodynamic stability requires constant control and verification of patient's needs, which is defined as personalized or goal-directed therapy.

Recent research has highlighted probable harmful effects of excessive administration of intravenous fluids, particularly in the elderly, patients with high comorbidity burden, and those undergoing extensive surgery (Raghunathan et al. 2015; Lobo and Awad 2014; Prowle et al. 2014; Varadhan and Lobo 2010; Walsh and Walsh 2005). The Enhanced Recovery Partnership and National Institute for Health and Care Excellence (NICE) guidelines recommend the fluid quality and quantity adjustment to the patient and procedure-related conditions. The goal-directed therapy aims at providing an oxygen carrier and adequate regional flow to optimize tissue perfusion. Cardiac output measurement during this therapy seems particularly relevant in patients undergoing major abdominal surgery (Saugel and Reuter 2018; Montenij et al. 2014). However, the mini-fluid challenge is often indicated as administering fluids just to increase rather than optimize stroke volume may lead to adverse complications. Excess fluid, particularly in abdominal surgery (AS), may accumulate in the lungs causing hypoxia, in the digestive tract causing nausea, delay the return of bowel motility, or decrease the stability of intestinal anastomoses (Wright et al. 2014; Kulemann et al. 2013; Marjanovic et al. 2009). Rational fluid therapy requires continuous monitoring. According to NICE and Enhanced-Recovery After Surgery (ERAS) recommendations, anaesthetists should be agile in using cardiac output measuring technologies in the intraoperative period (NICE 2013; Mythen et al. 2012; Tote and Grounds 2006). Nonetheless, the organizational and economic issues may hamper the compliance of intraoperative hemodynamic monitoring with the standards required by guidelines (Vincent et al. 2015; Cannesson et al. 2011). Fluid overloading remains prevalent in surgical patients, even in hospitals where the ERAS program has been introduced (Boersema et al. 2014; Warrillow et al. 2010). The UK authorities have recommended that all hospitals should have an intraoperative fluid protocol (NICE 2013). The first step in setting up a centre-specific protocol is to assess the current practice, including requirements, drawbacks, and possibilities. Therefore, in this study, we set out to evaluate the single-centre practice on intraoperative fluid therapy in patients undergoing AS, verify the methods used to guide therapy, and assess the possible influence of fluid regimen on treatment outcomes.

2 Methods

This study was based on the evaluation of medical files of 235 patients (103 men, 44%), aged 60 ± 15 years who underwent AS between September and November 2017. Reoperations were excluded. The variables assessed consisted of sex, age, body mass index (BMI), and type and duration of anaesthesia. The global procedural risk was assessed using the Surgical Mortality Probability Model (S-MPM) (Glance et al. 2012). This model has been developed for non-cardiac patients and includes the patient risk according to the American Society of Anaesthesiologists (ASA) physical status (ASAPS) classification system, procedural risk according to the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) guidelines, and the emergency of a procedure. The S-MPM

predicts the risk of early death in three classes: Class I – expected mortality <0.5%, Class II – expected mortality 1.5–4%, and Class III – expected mortality >10%. Patient confidentiality was ensured as the database was fully anonymized. The guidelines for reporting observational studies defined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement were applied in the study (von Elm et al. 2008).

Data on intraoperative fluid administration were evaluated concerning the quality (balanced crystalloids, saline, or colloids) and quantity (mL/kg/h of anaesthesia), including the fluids used as drug solvents. Systolic, diastolic, and mean arterial blood pressure (BP) and heart rate (HR) were evaluated at 5-min intervals before the induction, during the procedure, and postoperatively. The modified Aldrete score was used to assess post-anaesthesia care and the safety of patient discharge from the operating theatre. The prevalence of in-hospital death was part of the early prognostication.

Continuous data were expressed as medians and interquartile ranges (IQR). The Shapiro-Wilk test was used to verify data distribution. Categorical data were expressed as counts and percentages. Inter-group differences between continuous variables were assessed using the Mann-Whitney U or Kruskal-Wallis test. A Chi^2 test was used to assess differences between categorical variables. Correlations were assessed using the Spearman rank correlation coefficients. A p-value <0.05 defined the statistical significance of differences. The analysis was performed using a commercial MedCalc Statistical package v18.1 (Ostend, Belgium).

3 Results

One hundred and forty-nine (63.4%) patients were assigned to Class I according to the S-MPM scale, 67 (28.5%) to Class II, and 19 (8.1%) to Class III. The high-risk category included 124 (52.8%) patients, according to their functional status (i.e., ASA-PS Class 3+ or 3E) and 89 (38.0%) procedures (i.e., those with >5% procedural risk, according to ESC/ESA). Detailed characteristics of the study group and procedure-related parameters are depicted in Table 1. The median duration of anaesthesia was 175 (IQR 106–284) min. Two hundred and four patients (87.0%) scored on the Aldrete scale ≥9 points on discharge from the operating theatre. Eleven patients (4.7%) patients died during the initial hospitalization. The mortality rates in consecutive S-MPM classes were: 0.7%, 9%, and 21.1%, respectively. Detailed characteristics of performed procedures are depicted in Table 2.

The median fluid volume, irrespective of anaesthesia duration, was 10.4 (IQR 7.4–14.8) mL/kg/h. It was 9.1 (IQR 6.4–13.1) mL/kg/h for crystalloids [incl. 8.5 (IQR 5.6–11.0) mL/kg/h for balanced crystalloids and 0.9 (IQR 0.6–1.6) mL/kg/h for physiological saline], and 2.7 (IQR 1.7–3.8) mL/kg/h for synthetic colloids. In the shorter procedures of <175 min of anaesthesia duration, the median fluid volume was 11.5 (IQR 8.4–19.7) mL/kg/h. It was 11.0 (IQR 7.7–17.9) mL/kg/h for crystalloids [incl. 10.0 (IQR 6.6–16.0) mL/kg/h for balanced crystalloids and 1.0 (IQR 0.0–1.7) mL/kg/h for physiological saline]. In the longer procedures of >175 min of anaesthesia, the median fluid volume was significantly lower, amounting to 9.4 (IQR 7.0–12.6) mL/kg/h (Fig. 1), which was 7.6 (IQR 5.9–10.5) mL/kg/h for crystalloids [incl. 7.0 (IQR 5.0–9.2) mL/kg/h for balanced crystalloids and 0.6 (IQR 0.3–1.0) mL/kg/h for physiological saline] and 0.9 (IQR 0.0–2.3) mL/kg/h for synthetic colloids.

Although a total dose of administered fluids did not differ between the risk categories according to S-MPM, the patients who survived received significantly less fluid replacement than those who died [median fluid volume – 10.2 (IQR) 7.0-10.2) and 17.1 (IQR 14.0–21.4) mL/kg/h, respectively; $p = 0.001$]. This difference in fluid replacement between survivors and non-survivors concerned both crystalloids and colloids (Fig. 2). In the longer procedures, the fluid volume was higher in S-MPM Class II and Class III than in Class I ($p = 0.01$) (Fig. 3). Patients who died received more fluids only in case of longer procedures ($p = 0.004$).

A greater than 100 mL intraoperative bleeding was reported in 75 patients. The median volume of lost blood in these subjects reached 500 (IQR

Table 1 Patients' characteristics

Variable		n (%) Median (IQR)
Sex	Male	103 (44.0%)
	Female	132 (56.0%)
Age (years)	Median (IQR)	60 (46–67)
	<60	115 (48.9%)
	≥60	120 (51.1%)
BMI (kg/m^2)	Median (IQR)	26 (22–29)
	Underweight (<18.5)	15 (6.4%)
	Normal (18.5–25.0)	87 (37.0%)
	Overweight (≥25)	133 (56.6%)
ASA-PS	Class I	25 (10.6%)
	Class II	98 (41.7%)
	Class III	91 (38.7%)
	Class IV	20 (8.5%)
	Class V	1 (0.5%)
	Class VI	0 (0.0%)
	Emergency surgery – E	34 (14.5%)
Patient-risk category (ASA-PS)	Low risk (class 1–2)	111 (47.2%)
	High risk (class 3–5 or E)	124 (52.8%)
Procedural-risk category (ESC/ESA)	Low	53 (22.5%)
	Moderate	93 (39.5%)
	High	89 (38.0%)
S-MPM	Class I	149 (63.4%)
	Class II	67 (28.5%)
	Class III	19 (8.1%)
Time of anaesthesia (min)	Median (IQR)	175 (108–283)
	Shorter (<175 min.)	114 (48.5%)
	Longer (≥175 min.)	121 (51.5%)
Type of anaesthesia	General anaesthesia	227 (96.6%)
	TIVA	3 (1.3%)
	Regional anaesthesia	3 (1.3%)
	Local anaesthesia	2 (0.8%)
Hospitalization length (days)	Median (IQR)	6 (2–10)
	Shorter (< 6 days)	108 (46.0%)
	Longer (≥ 6 days)	127 (54.0%)
Mortality		11 (4.7%)

BMI body mass index, *ASA-PS* American Society of Anaesthetists (ASA) physical status classification, *ESC/ESA* European Society of Cardiology/European Society of Anaesthesiology, *IQR* interquartile range, *S-MPM* Surgical Mortality Probability Model, *TIVA* Total intravenous anaesthesia

225–675) mL. A volume of lost blood was associated with the administered volumes of red blood cells concentrate (RBCC) ($r = 0.63$; $p < 0.001$), fresh frozen plasma (FFP) ($r = 0.45$; $p < 0.001$), and colloids ($r = 0.50$; $p < 0.001$). RBCC was transfused in 16 and FFP in 11 patients. Patients with higher intraoperative blood loss were more likely to belong to ASA-PS Class 3+ ($p < 0.01$). There was an inverse association between BMI and the total fluid dose ($r = -0.40$; $p < 0.01$). The volume of fluids was independent of the sex or age of patients.

Blood pressure was monitored non-invasively in 229 (97%) and invasively in 6 (3%) patients, with fluid therapy guided by the arterial-blood gas

Table 2 Distribution of patients by surgical procedures. Open surgery was performed in 178 (75.7%) of cases and laparoscopic surgery in 57 (24.3%) of cases

Type of surgery	n (%)	Anatomical area	n (%)
Distal pancreatectomy	24 (10.2%)	Pancreas	61 (26.0%)
Pancreatoduodenectomy	21 (8.9%)		
Total pancreatectomy	4 (1.7%)		
Pancreatic cyst surgery	12 (5.1%)		
Palliative biliary/gastric bypass surgery	8 (3.4%)	Stomach	19 (8.1%)
Subtotal/total gastrectomy	11 (4.7%)		
Oesophagectomy	9 (3.8%)	Oesophagus	9 (3.8%)
Cholecystectomy	33 (14.0%)	Gallbladder/biliary tract	33 (14.0%)
Appendectomy	9 (3.8%)	Appendix	9 (3.8%)
Small intestine resection	5 (2.1%)	Incision, excision, and anastomosis of intestine	39 (16.6%)
Restoration of gastrointestinal continuity	9 (3.8%)		
Hemicolectomy	10 (4.3%)		
Sigmoidectomy	15 (6.4%)		
Proctectomy	8 (3.4%)	Rectum, rectosigmoid, and perirectal tissue	13 (5.5%)
Perianal abscess	5 (2.1%)		
Pancreas/biliary biopsy	4 (1.7%)	Open biopsy	6 (2.6%)
Lymph node biopsy	2 (0.9%)		
Hernia repair surgery	31 (13.2%)	Hernia repair	31 (13.2%)
Pelvic tumour surgery	2 (0.9%)	Other abdominal areas	15 (6.4%)
Intraperitoneal abscess/eventration	10 (4.3%)		
Splenectomy	3 (1.3%)		
Total	235 (100%)		235 (100%)

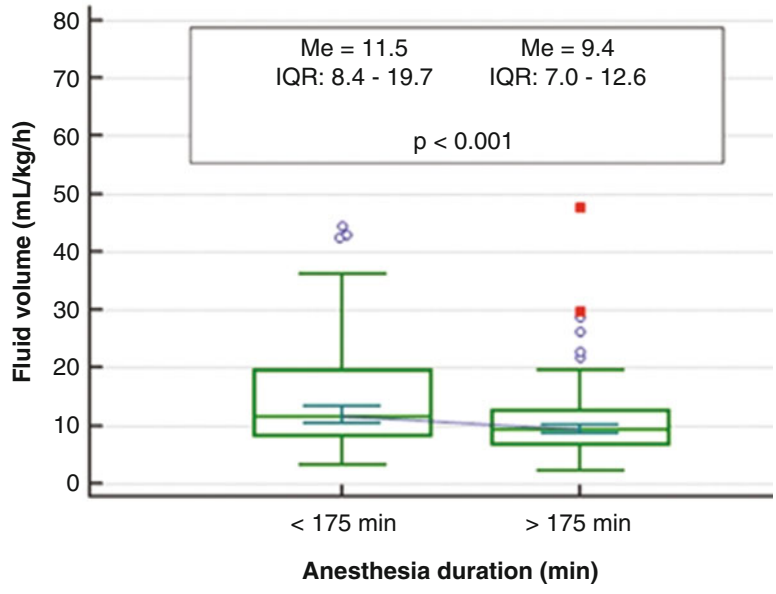

Fig. 1 Total fluid replacement by the length of anaesthesia during abdominal surgery. Circles denote outlier observations and squares denote extreme observations; *Me* median, *IQR* interquartile range

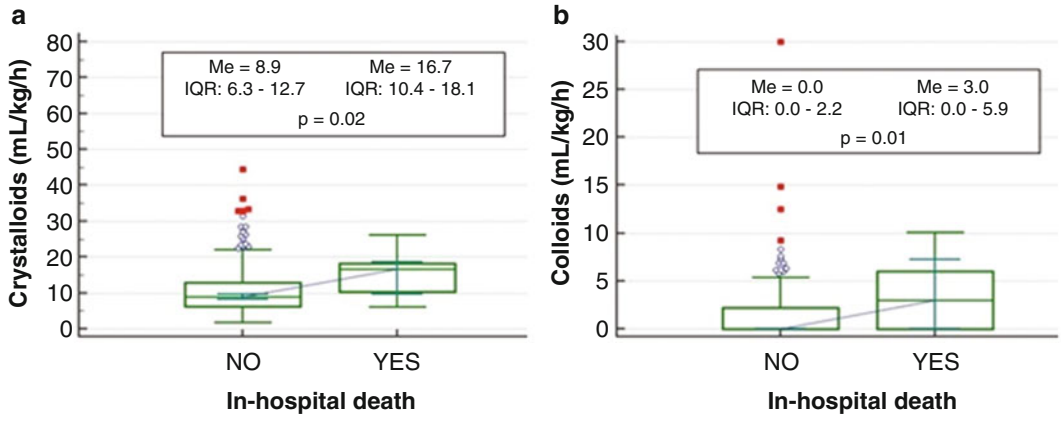

Fig. 2 Total crystalloid (**a**) and colloid (**b**) fluid replacements in patients who survived or died during the hospital stay. Circles denote outlier observations and squares denote extreme observations; *Me* median, *IQR* interquartile range

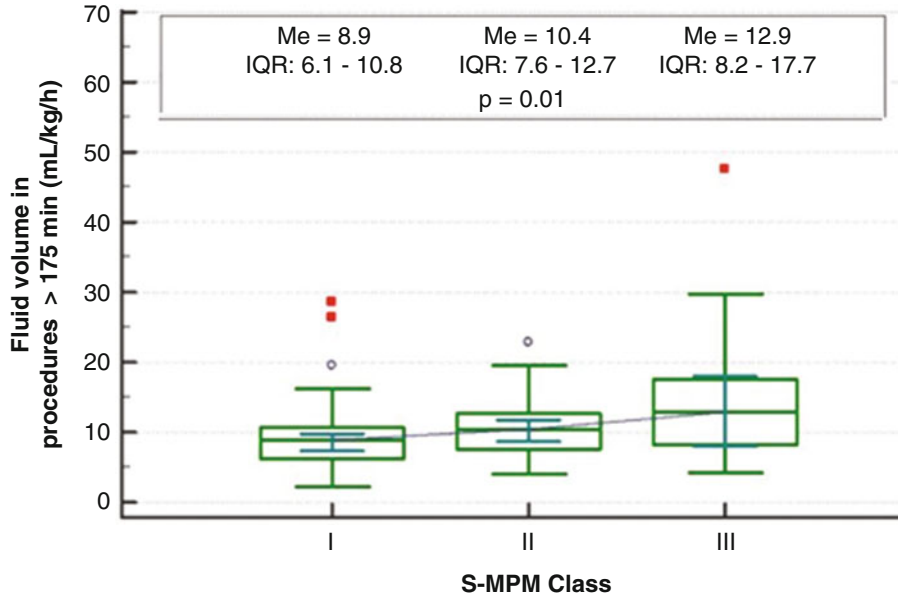

Fig. 3 Total fluid replacement in abdominal surgery lasting for more than 175 min by the Surgical Mortality Probability Model (S-MPM) class. Circles denote outlier observations and squares denote extreme observations; *Me* median, *IQR* interquartile range

content (2% S-MPM Class I, 1.5% Class II, and 10.5% Class III patients). In 100 patients (42.6%), central venous pressure was directly measured. Central venous access was established more frequently in high-risk patients undergoing high-risk procedures ($p < 0.01$) and in procedures lasting $\geq$175 min ($p < 0.01$). The central venous catheter was placed in 32.2%, 59.7%, and 63.7% of patients in S-MPM Class I, II, and III, respectively ($p < 0.01$).

4 Discussion

The main goal of the study was to evaluate intraoperative fluid therapy and its monitoring in a tertiary hospital. We revealed that although fluid therapy was rather liberal, it was adjusted to the risk and duration of a procedure. The monitoring was mainly based on a non-invasive assessment of mean blood pressure. It is worthwhile to note that patients who died in the hospital received more fluids, whereas the S-MPM class-scale was unreliable in predicting the volume of fluids administered. Nonetheless, the observational nature of the study made it impossible to draw cause-effect conclusions.

Intraoperative haemodynamic optimization using fluid therapy has been long since discussed by international clinical bodies. The first issue to focus on is the selection of fluid. It has been documented that the fluids of choice are crystalloids, especially those balanced or buffered (Feldheiser et al. 2016). The physiological saline should be used with caution as its irrational use is associated with an increased risk of hypernatremia, hyperchloremia, metabolic acidosis, and acute kidney injury (Myles et al. 2017; Lobo and Awad 2014). In the present study, we followed the recommendations to this end and used physiological saline mainly as a drug solvent. The use of synthetic colloids is still debatable and their role in intraoperative medicine remains to be verified by the PHOENICS (Prospective, randomized, controlled, double-blind, multi-centre, multinational study on the safety and efficacy of a 6% Hydroxyethyl starch sOlution versus an Electrolyte solutioN In patients undergoing eleCtive abdominal Surgery) study scheduled to be completed in July 2020 (Wittenstein et al. 2018).

Balanced intraoperative fluid therapy is essential as both fluid overload and underload could adversely affect treatment outcomes (Bellamy 2006). Recently, a combination of patient-tailored therapy with precise hemodynamic management protocols (PPPHM) has been postulated (Saugel and Vincent 2019). The development of surgical techniques has significantly reduced bleeding and fluid loss by evaporation from the abdominal cavity during surgery (Miller and Myles 2019). The implementation of the enhanced recovery after surgery (ERAS) protocols, which aims at the preoperative correction of fluid deficits, judicious fluid withdrawal before anaesthesia, and the maintenance of fluid balance close to zero, prescribes a restrictive approach to intraoperative fluid therapy, although the matter is somehow contentious. The large multi-centre RELIEF study has demonstrated a relationship between restrictive fluid therapy and a greater incidence of acute kidney injury (Myles et al. 2018). Likewise, Brandstrup (2018) has suggested that a moderately liberal fluid therapy protocol is safer than a restrictive one. Thus, it is recommended to maintain an overall positive fluid balance of 1 L to 2 L, which corresponds to a crystalloid fluid volume of 10 mL/kg/h to 12 mL/kg/h during extensive surgical procedures (Miller and Myles 2019). Our present results are consistent with this recommendation, especially as the delivery of fluids was risk-adjusted during long procedures.

Both NICE and ERAS guidelines emphasize the importance of proper intraoperative hemodynamic monitoring (i.e., cardiac output measurement) to ensure adequate tissue perfusion (Feldheiser et al. 2016; NICE 2013; Mythen et al. 2012). The selection of monitoring techniques in the surgical setting, especially in the context of body fluid maintenance, is debatable (Xu et al. 2018; Sun et al. 2017; Rollins and Lobo 2016). The OPTIMISE and FEDORA studies have shown a significant reduction in the risk of complications and shortened hospitalizations resulting from the implementation of targeted therapy (Calvo-Vecino et al. 2018; Pearse et al. 2014). The choice of a monitoring technique is determined by the patient's condition, estimated global perioperative risk, and organizational and economic possibilities. Referring to the physician's preferences, a study encompassing 368 European and American anaesthesiologists has demonstrated that 34% of them monitor cardiac output during anaesthesia and more than 80% of those who do use the central venous pressure measurement (Cannesson et al. 2011).

Somehow in line with those data, the EuSOS study found that only 1 in 10 patients in Europe undergoing major abdominal surgery is monitored for cardiac output (Ahmad et al. 2015). Our present observation was that 100 (42.6%) patients had a central venous catheter placed to monitor venous pressure and another 6 (2.7%) had an arterial catheter placed to monitor real-time BP and blood lactate level. However, it looks that many more patients required such monitoring as almost one half were classified as ASA-PS Class 3 or higher and 38% of surgeries were high-risk procedures. Noticeably, broadened haemodynamic monitoring has been found both clinically beneficial and cost-effective. Additional expenditures it requires are compensated by limiting the costs of treatment of complications and reducing hospitalization length (Ebm et al. 2014). The in-hospital mortality rate in our study reached 4.7%, which appears consistent with the multi-centre cohort data on postoperative mortality in Europe (Pearse et al. 2012).

The present study has some limitations. First, our observations are from a single-centre, and only the patients were included who had abdominal surgery in the preceding 3 months. On the other side, homogeneity of the examined group enhanced the reliability of results obtained and allowed for standardization of intraoperative procedures performed. Second, there was a relatively small intraoperative blood loss in our patients making surgical bleeding of secondary importance in determining fluid therapy. Nevertheless, we considered transfused blood products in the volume calculation, including them among colloidal solutions. Third, the evaluation of fluid therapy did not cover pre- and post-operative conditions. Reliable monitoring and correction of fluid balance in the whole intraoperative period (i.e., from admission to discharge from the hospital) were made difficult by shared responsibilities in the process by anaesthetists, surgeons, and the patient's family caregivers. Fourth, haemodynamic monitoring in the operating theatre is pricey, which eventually takes a toll on the implementation of international recommendations to this end in less well-to-do societies.

In conclusion, we herein reviewed the principles of fluid replacement therapy in patients undergoing a spectrum of abdominal surgeries in a tertiary hospital in Poland. The therapy was liberal but complied with the international recommendations concerning the type of fluid. It consisted of balanced crystalloids and was adjusted to the intraoperative risk. Haemodynamic monitoring was suboptimal. Fluid replacement therapy requires optimization and a standardized approach consistent with treatment requirements.

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Conflicts of Interest The authors declare no conflict of interest concerning this article.

Ethical Approval This review article is based on a backstage evaluation of anonymous medical files. Therefore, it is non-interventional and does not contain any studies with direct human participation.

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Manual Pressure Release and Low-Grade Electrical Peripheral Receptor Stimulation in Nonspecific Low Back Pain: A Randomized Controlled Trial

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Abstract

Chronic nonspecific low back pain is a frequent clinical condition affecting the general population and influencing disability level and quality of life. We performed a single-blinded, randomized, and controlled study to compare the effectiveness of manual pressure release (MPR) and electrical neuromodulation (ENM) treatments in the management of chronic low back pain. There were 20 patients with chronic low back pain randomly assigned to 6 treatment sessions with either technique. Both groups were treated for 2 days a week for 3 weeks. Myofascial trigger points (MTrPs) were identified and skin conductance, pressure-pain threshold, postural changes, and the Oswestry Disability Index were assessed before and after each treatment session, along with the protocol-end data compared against the baseline data in each group. We found an outstanding and about equal deactivation of MTrPs from pre- to post-treatment in both groups, reducing disability in patients with chronic low back pain. The study highlights the ENM as a reliable tool for the evaluation of MTrPs, given a high agreement with the MPR. The effect on the neuromuscular condition of treating the "key trigger points" found in this study advances the knowledge of medical rehabilitation.

Keywords

Electrical neuromodulation · Low back pain · Manual pressure release therapy · Myofascial trigger points · Rehabilitation · Skin receptor stimulation

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1 Introduction

The pain between the costal margins and the folds of the lower gluteus muscle is defined as chronic nonspecific low back pain (LBP) when it is unrelated to clinical conditions such as osteoarthritis

of the facet joints, degenerative disc diseases, spinal stenosis, or musculoskeletal disorders (Iglesias-González et al. 2013). The prevalence of low back pain in the general population is roughly estimated at 10–60% depending on patient selection criteria (Cecchi et al. 2006). A highly variable prevalence may stem from turbid and still unsettled criteria defining the diagnosis of chronic low back pain (Cedraschi et al. 1999). The pain adversely affects the quality of life decreasing the functional status and limiting working agility, which causes a substantial economic burden (Di Iorio et al. 2007).

It has been proposed that myofascial trigger points (MTrPs), described as palpable hyperirritable nodules in a skeletal muscle or fascia (connective tissue), are involved in chronic low back pain pathways. These nodules are a source of pain (active) upon muscle action or when stimulated electrically or manually by compression (latent) (Shah et al. 2015). Somatic impairment accompanying chronic low back pain is characterized by myofascial and proprioceptive dysfunction present in peripheral dermatomes, with pain pointing to pathology in related nerve roots involving the central sensitization mechanism (Bellomo et al. 2016; Schäfer et al. 2009). Besides the use of palpation in the pain area, there are no accepted criteria to identify MTrPs. Recently, electrical neuromodulation, performed through an electro-neuro feedback device, an instrument characterized by biphasic sinusoidal signal, has been proposed as a treatment method concerning for dysfunction of MTrPs (Barassi et al. 2019; Bellomo et al. 2016).

Neural, immunologic, and endocrine properties of the skin create an integrated relay that modulates peripheral sensory and autonomous nervous systems, actuating the central sensitization mechanism. In pathological conditions, like chronic low back pain, the relay may alter the galvanic skin response (Jayanthi et al. 2015). The electrical neuromodulation converts the galvanic cutaneous variations in electrical signals, which represents a reliable index of the relationship between the neural system and biological structures such as muscles, joints, or viscera.

Postural abnormalities are frequently reported in association with chronic low back pain, despite the consensual lack of a definition of what is normal posture (Bassani et al. 2019; Pokorski et al. 2018). Such abnormalities come to light in static and dynamic postural analyses. For example, a Tanzanian case-control study has reported an anteversion of the pelvic angle and a postural thoracic kyphosis in subjects affected by low back pain when compared to control painless subjects (Tatsumi et al. 2019). Other studies have reported that spinopelvic motions might be altered during low back pain due to disturbed cerebral motor control of postural adjustment outpacing the arm movements (Sung et al. 2020; McDowell et al. 2018).

Based on the aforementioned considerations, the objectives of the present study were to evaluate the diagnostic concordance between the manual pressure-release (MPR) and instrumental electro-neuromodulatory (ENM) treatments of dysfunctional somatic areas represented by key MTrPs and compare the effectiveness of these two rehabilitative intervention techniques in chronic low back pain treatment. The consideration was directed to postural assessment, ENM impedance, and pain and disability levels.

2 Methods

2.1 Patients and Study Design

This study was a single-center, single-blinded, randomized, 3-week, and two parallel arm clinical trial. It was conducted at the Center for Physiotherapy, Rehabilitation and Re-Education of the Center of Sports Medicine of the "G. d'Annnunzio" University in Chieti, Italy. There were 20 patients enrolled in the study (11 males and 9 females) diagnosed with chronic low back pain. The mean age of patients was 51.6 ± 5.0 years. They were randomly assigned to two intervention groups treated with MPR and ENM. The diagnosis was based on the presence of pain of light-to-moderate intensity between the costal margins and the inferior gluteal folds, continuously lasting for more than 1 month and variably present for at least

3 years before the enrollment. The sorting of chronic low back pain patients was based on the description provided in the work of Bardin et al. (2017). Exclusion criteria consisted of the presence of low back pain clearly associated with a diagnosis of radicular syndrome or lumbar disk herniation, a history of corticosteroid treatment, immunologic disorders, previous spinal surgery, spine trauma or fracture, bladder and bowel dysfunctions, weakness or loss of sensation in lower extremities, and a history of mental health disorders that could limit adherence to the study procedures. MTrPs were assessed pre-post treatment at each session while the Oswestry Disability Index (ODI), computerized postural evaluation, and digital pressure algometry were performed at baseline before the first session and after the final session of the study.

2.2 Myofascial Trigger Points (MTrPs)

MTrPs detection and intervention were performed according to criteria described by Travell and Simons (1983). MTrPs were identified as palpable tense nodules or hyperirritable points in the taut band of a skeletal muscle. They were considered active when caused referred pain perceived at a location other than the site of the stimulus or inactive or latent when caused a focal muscle twitch or tenderness and stiffness on compression. The MTrPs assessment was conducted by two independent rehabilitators, each using both MPR and ENM treatments, in a blinded fashion after a 30-min patient's rest. The evaluation sequence between MPR and ENF was randomly determined to avoid a potential carry-over effect. MPR and ENM interventions were used for peripheral stimulation of "key trigger points" identified as the points of the highest grade of dysfunctionality according to the greater first reaction value found by ENM and a greater change perceived by MPR in local tension associated with a reduction of motion range and pain. There were two sessions of treatment a week, each lasting for 30 min, for a total of 3 weeks, performed by the same rehabilitators. The clinical protocol was the same in both MPR and ENM groups.

2.3 Assessment of Low Back Pain

Disability Scale Oswestry Disability Index (ODI) was used to evaluate the low back pain disability. The score ranges from 0 to 100. The higher the score the greater is disability, with a score of 0–20 reflecting minimal disability.

Posture Postural balance was evaluated using a human motion capture system equipped with an RGB-IR (red, green, and blue-infra red) camera capable of capturing frames in 3D and Sa.B.B. Kinect® software (Microsoft Co, Redmond, Washington DC). The system provides both visual and functional information, using sensors capable of identifying 20 reference points of the patient's body in 20 s. The data are acquired in the upright position while the patient observes a reference point in front of him. The software works with a frequency of 30 frames *per* second and every single analysis has a total duration of 5 s, with an average acquisition of 150 frames. It creates a 3D avatar, called "visual skeleton", which is graphically represented in frontal and sagittal projections and quantifies the structural misalignment of the back-lumbar spine (Barassi et al. 2016).

Pressure-Pain Algometry The referred pressure-pain threshold in MTrPs was evaluated on the lumbar dermatomes of the paraspinal, quadratus lumborum, and piriformis muscles using a digital pressure algometer (F-Meter; Storz Medical AG, Tägerwilen, Switzerland). The device was pointed locally in the region of interest, with step increases in the pressure of 200 g applied by the operator until the pain was evoked; the point marking the pressure-pain threshold.

2.4 Manual Pressure Release (MPR): Examination and Intervention

MTrPs were detected by palpation of muscle bellies, searching for tense nodules or hyperirritable points with a local or referred pain pathway. Patients were asked to relax in the supine position for 5 min, and then the following muscle points were bilaterally assessed: pectoralis major (C5-T1), rectus abdominis (T5-L1), rectus femoris (L2-L4), adductor magnus (L2-L5), tibialis anterior (L4-S1), adductor halluces (L4), quadratus plantae (L5), and abductor quinti digiti (S1). Subsequently, the position was changed to prone and the other muscle points were assessed: splenius cervicis, upper and lower trapezius (C2-C4), paraspinal longissimus dorsi (T10-L5), quadratus lumborum (T12-L3), gluteus (L5-S2), gastrocnemius, soleus, and hamstrings (L4-S1). After the MTrPs were detected, a gentle and sustained local pressure was applied on them with a finger, usually for no more than 30 s, up to the moment of muscle relaxation.

2.5 Electrical Neuromodulation (ENM): Examination and Intervention

The two-electrode ENM device (ENF-Studio Physio; Fast Therapies S.r.l.; Carpenedolo, Italy) applied low-electrical biphasic, sinusoidal, damped impulses, similar in morphology to the ECG, delivered by two surface electrodes. Skin impedance was recorded avoiding the interference of feedback peripheral and central adaptative processes. The first reaction value was computed for every MTrPs and a map of detections was done. The first reaction is a dimensionless parameter expressing an increased electrical conductivity of the skin. In a trial experiment performed in the MPR group, therapeutic effects of ENM could be divided into three separable phases: (1) severe pain relief lasting for about 3 min, capable of desensitizing the nociceptors of the dysfunctional area and reducing pain perception; (2) muscle decontracting lasting for about 5 min, producing relaxation of muscle fibers; and (3) superficial draining lasting for 3 min, causing the outflow of extracellular imbibition in the MTrPs.

All measurements were done in duplicate and the average was taken as a final result.

2.6 Statistical Elaboration

Concordance Between Manual Pressure Release (MPR) and Electrical Neuromodulation (ENM) Treatments The concordance between the two methods was assessed using Kendall's tau coefficient and 95% confidence intervals (95%CI). Moreover, considering the manual examination as a reference, a logistic model was used to graph receiver operating curve (ROC) curves, with adjustments for session and intervention.

Clinical Trial Analysis Data were expressed as mean ± SD, and as counts and frequencies. The linear mixed model was used to analyze variations in the values of the muscle first reaction, ODI, pressure-pain algometry, and postural misalignment in the pre-post session in either intervention group. The model enhances the precision of repeated measurement analysis by using all combined information that also includes missing data (Singer 1998). Statistical tests were two-sided, and a p-value <0.05 defined the significance of differences. The analysis was conducted using a commercial SAS v9.4 statistical package (SAS Institute Inc., Cary, NC).

3 Results

3.1 Concordance Between Manual Pressure Release (MPR) and Electrical Neuromodulation (ENM) Treatments

Out of the 4080 dermatome evaluations (6 sessions for 20 patients for 34 areas related to 34 muscles assessed), a close agreement was

found between MPR and ENM interventions concerning the identification of two most dysfunctional (key) MTrPs that required treatment. These sites were identified in different investigated muscles in each patient; Kendall's tau was 0.70 (95%CI: 0.65–0.75; $p < 0.001$) and did not change appreciably when weighted by the number of sessions. For the MPR, used as a gold standard, the area under the ROC curve amounted to 0.85, with the adjustments for treatment and session. In detail, a complete agreement between the two methods was achieved in 3824 (93.7%) muscle assessments while the remaining 256 (6.3%) were non-concordant assessments.

3.2 Clinical Trials

The pre-post treatment data on the first reaction value in 17 muscle dermatomes obtained from the MPR and ENM evaluations are reported in Table 1. We mostly found insignificant differences between the two intervention groups concerning

Table 1 Myofascial trigger points (MTrPs) in muscle dermatomes assessed as the first reaction value during the ENM evaluation in patients (n = 20) with nonspecific low back pain at baseline (pre) and after (post) the last treatment session of the manual pressure release (MPR) and electrical neuromodulation (ENM) interventions

	MPR		ENM				
Muscle dermatomes	Pre	Post	Pre	Post	p-value[1]	p-value[2]	p-value[3]
Pectoralis major (C5-T1)	5.98 ± 0.41	2.36 ± 0.50	3.31 ± 0.50	3.47 ± 0.55	0.110	<0.001	0.260
Rectus abdominis (T5-L1)	5.45 ± 0.57	2.52 ± 0.58	3.90 ± 0.60	3.26 ± 0.59	0.380	0.050	0.480
Rectus femoris (L2-L4)	3.01 ± 0.36	1.43 ± 0.35	2.78 ± 0.38	2.72 ± 0.37	0.006	0.020	0.005
Adductor magnus (L2-L5)	3.31 ± 0.35	1.95 ± 0.36	1.89 ± 0.38	1.97 ± 0.38	0.990	0.040	0.040
Tibialis anterior (L4-S1)	3.18 ± 0.35	1.53 ± 0.35	2.90 ± 0.37	1.98 ± 0.36	0.310	0.240	<0.001
Adductor allucis (L4)	7.68 ± 0.78	2.33 ± 0.80	4.86 ± 0.80	6.58 ± 0.85	<0.001	<0.001	0.980
Abductor quinti digiti (S1)	3.87 ± 0.75	1.75 ± 0.74	6.15 ± 0.75	6.74 ± 0.79	<0.001	0.050	0.007
Quadratus lumborum (T12-L3)	5.01 ± 0.98	2.17 ± 0.98	8.64 ± 1.04	6.29 ± 1.03	0.003	0.800	0.030
Splenius cervicis (C2-C4)	13.18 ± 1.08	3.30 ± 1.84	12.12 ± 1.15	5.03 ± 1.14	0.250	0.200	0.110
Upper trapezius (C2-C4)	6.97 ± 0.80	2.61 ± 0.79	9.74 ± 0.85	5.14 ± 0.84	0.030	0.880	0.190
Lower trapezius (C2-C4)	4.00 ± 0.63	2.10 ± 0.61	7.98 ± 0.66	3.69 ± 0.67	0.080	0.070	0.280
Paraspinal/ longissimus dorsi (T10-L5)	6.80 ± 0.79	2.52 ± 0.80	8.22 ± 0.84	3.65 ± 0.82	0.330	0.870	0.980
Gluteus (l5-S2)	5.70 ± 0.76	1.83 ± 0.76	7.67 ± 0.80	3.62 ± 0.80	0.100	0.870	0.060
Hamstrings (L4-S1)	4.18 ± 0.64	2.03 ± 0.63	5.94 ± 0.67	2.62 ± 0.68	0.480	0.320	0.005
Gastrocnemius (L4-S1)	7.40 ± 0.74	1.57 ± 0.75	2.27 ± 0.79	1.72 ± 0.79	0.040	<0.001	0.350
Soleus (L4-S1)	3.62 ± 0.38	1.63 ± 0.38	3.21 ± 0.40	1.67 ± 0.39	0.940	0.540	0.030
Quadratus plantae (L5)	12.52 ± 0.94	3.10 ± 0.94	8.81 ± 0.99	3.54 ± 0.99	0.740	0.030	0.400

Data are means ±SD

p-value[1]—comparison between the MPR and ENM intervention groups

p-value[2]—interaction between pre-post effects in each single session and intervention group

p-value[3]—interaction between pre-post (baseline vs. after 6 treatment sessions) and intervention group

Table 2 Oswestry Disability Index (ODI) at baseline (pre) and after the last treatment session (post) of the manual pressure release (MPR) and electrical neuromodulation (ENM) interventions

	MPR		ENM				
	Pre	Post	Pre	Post	p-value[1]	p-value[2]	p-value[3]
ODI score	27.6 ± 2.9	8.6 ± 2.9	20.3 ± 3.0	9.7 ± 3.0	0.700	0.007	0.120

Data are means ±SD
p-value[1]—comparison between the MPR and ENM intervention groups
p-value[2]—comparison between the pre-post treatment time in either group
p-value[3]—interaction between treatment time (baseline vs. after 6 treatment sessions) and intervention group

Table 3 Pressure-pain threshold assessed with a digital pressure algometer at baseline (pre) and after the last treatment session (post) of manual pressure release (MPR) and electrical neuromodulation (ENM) interventions. Each unit of pressure-pain threshold corresponds to a weight of 200 g

	MPR (1 = 200 g)		ENM (1 = 200 g)				
Muscle dermatomes	Pre	Post	Pre	Post	p-value[1]	p-value[2]	p-value[3]
Paraspinal right	15.3 ± 2.9	24.8 ± 2.9	16.8 ± 2.90	26.6 ± 2.9	0.640	0.020	0.960
Paraspinal left	15.0 ± 3.3	25.6 ± 3.3	16.4 ± 3.2	26.7 ± 3.3	0.810	0.030	0.960
Quadratus lumborum right	13.4 ± 2.7	24.4 ± 2.7	12.4 ± 2.7	16.3 ± 2.7	0.050	0.230	0.130
Quadratus lumborum left	14.8 ± 3.6	27.7 ± 3.5	12.1 ± 3.5	18.9 ± 3.5	0.050	0.090	0.270
Piriformis right	13.4 ± 3.4	19.0 ± 3.5	14.9 ± 3.4	28.6 ± 3.5	0.030	0.001	0.160
Piriformis left	12.6 ± 3.0	21.6 ± 3.1	17.0 ± 3.0	29.6 ± 3.1	0.050	0.003	0.520

p-value[1]—comparison between the MPR and ENM intervention groups
p-value[2]—comparison between the pre-post treatment time in either group
p-value[3]—interaction between treatment time (baseline vs. after 6 treatment sessions) and intervention group

the general treatment efficacy for the following muscles: tibialis anterior, splenius cervicis, upper trapezius, lower trapezius, paraspinal/longissimus dorsi, gluteus, and the soleus. However, there were significant interactions between the intervention groups and the pre-post treatment effects in each single session in dermatomes of the following muscles: pectoralis major (<0.001), rectus abdominis ($p = 0.050$), rectus femoris ($p = 0.020$), adductor magnus ($p = 0.040$), adductor allucis ($p < 0.001$), abductor quinti digiti ($p = 0.050$), gastrocnemius ($p < 0.001$), and the quadratus plantae ($p = 0.030$). In all these dermatomes, the MPR resulted in a greater increase in the pre-post pressure-pain threshold than the ENM did. Besides, there was a significant interaction between the intervention groups and the pre-post changes taking the six treatment sessions together in the following dermatomes: rectus femoris ($p = 0.005$), adductor magnus ($p = 0.040$), tibialis anterior ($p < 0.001$), abductor quinti digiti ($p = 0.007$), quadratus lumborum ($p = 0.030$), hamstrings ($p = 0.005$), and the soleus ($p = 0.030$).

Table 2 compares the ODI score in patients subjected to MPR and ENM interventions at baseline and after the study ending session. Overall, the patients showed minimal-to-moderate disability at baseline, with inappreciable differences between the intervention groups. A significant score reduction was demonstrated after the last session in both groups ($p = 0.007$).

The level of pain was assessed at baseline and after the sixth ending session in both intervention groups, using a pressure algometer. Data were obtained bilaterally on three muscles: paraspinal, quadratus lumborum, and piriformis. There was a significant increase in the minimum pressure (strength) needed to induce pain, bilaterally, for the dermatomes referable to the paraspinal and piriformis muscles, regardless of the intervention type, with inappreciable differences for the interaction between the time of treatment (pre-post) and the intervention group (Table 3).

Finally, there were no significant differences between the two treatments concerning the postural asymmetry measured at bis-acromial, bis-iliac, and patellar levels and expressed as the

Table 4 Postural changes assessed with a human motion capture system at baseline (pre) and after the last treatment session (post) of the manual pressure release (MPR) and electrical neuromodulation (ENM) interventions

	MPR (°)		ENM (°)				
Joint level	Pre	Post	Pre	Post	p-value[1]	p-value[2]	p-value[3]
Bis-acromial line	1.5 ± 0.3	0.8 ± 0.3	1.3 ± 0.3	1.0 ± 0.3	0.760	0.440	0.550
Bis-iliac line	1.4 ± 0.3	1.4 ± 0.3	1.2 ± 0.3	0.7 ± 0.3	0.130	0.330	0.500
Patellar line	5.9 ± 2.5	5. 1 ± 2.5	7.4 ± 2.4	4.8 ± 2.4	0.930	0.410	0.680

p-value[1]—comparison between the MPR and ENM intervention groups
p-value[2]—comparison between the pre-post treatment time in either group
p-value[3]—interaction between treatment time (baseline vs. after 6 treatment sessions) and intervention group

inclination angle of the line passing through the center of each joint at the level referring to the ideal horizontal line (Table 4).

4 Discussion

This study highlights the ENM as a reliable tool for the evaluation of MTrPs in patients with chronic low back pain, given a high agreement with the manual evaluation. Additionally, the ENM showed a broader modulating effect in the myofascial syndrome in some dermatomes (L2-S1), whereas the effects resembled those of a traditional manual approach in dermatomes of the pectoralis, rectus femoris, and gastrocnemius muscles. Further, both treatments reduced the ODI score and enhanced the pressure (strength) threshold for pain induction in an equal manner. The postural examination carried out at study onset and end showed a tendency for a reduction in the frontal plane degree of inclination of shoulders, pelvis, and knees, which speaks for improvement in the general postural structure. This change was somewhat more pronounced in patients treated with ENM than those with MPR, although the differences were not statistically significant. Stimulation of skin receptors by ENM treatment alone suffices to obtain the neurovegetative results like those seen during MPR stimulation. This is attributable to the remodeling of intersegmental circuits at the level of the dorsal horns through a series of impulses that are guided as afferent signals reaching the spinal cord (Barassi et al. 2018). This series of events could lead to fluidization and decongestion of incoming neural information. Congestion of such information may affect the neuronal motor output, which finds their somatic expression in myofascial dysfunction and nociceptive perturbation in the skin.

The main limitation of this study was a small sample of patients with chronic low back pain. Complex study design and duplicate measurements of indices performed in each session made it difficult to enlarge the population of patients. Another limitation was a single-blinded procedure, but the execution of physiotherapy made it impossible to blind therapists. To counter the possible investigators' bias, the identity of the two rehabilitative treatments was blinded for the statistical elaboration. The disability of chronic low back pain was assessed based on the ODI score alone. This index is subject to concerns related to the cross-cultural validity, the one-dimensional nature of the scale, and a poor ability to distinguish patients with low (floor effect) and high (ceiling effect) levels of disability (Lee et al. 2017). Patients enrolled in this study showed a low degree of disability, in both groups alike. In this context, the possibility of a random error appears small (Brodke et al. 2017; Lu et al. 2013).

In conclusion, the findings of this study demonstrate the effectiveness of both manual pressure release and electrical neuromodulation treatment in the management of chronic nonspecific low back pain. Both rehabilitative techniques reduce patients' disability. The study highlights the electrical neuromodulation, by far little recognized, as a reliable alternative for the evaluation of myofascial trigger points, given a high agreement with the results of manual evaluation. Notably, in accord with other research (Tozzi 2015a; Tozzi

2015b), it appears that treating just the two most dysfunctional sites in the main muscles, identified as the "key trigger points" by either electrical neuromodulation or manual pressure release technique, leads to functional neuromuscular improvement. The influence on the neuromuscular condition of treating the "key trigger points" brought to light in this study creates new physiotherapeutic schemes that advance medical rehabilitation and warrant further research using alternative study designs.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

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Human Inhalation Study with Zinc Oxide: Analysis of Zinc Levels and Biomarkers in Exhaled Breath Condensate

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Abstract

Workers in the zinc processing, for example, welding or hot-dip galvanizing, are exposed to aerosols consisting of particles and gases, including zinc oxide (ZnO), which can affect human health. In this study, we addressed the effects of short-term controlled exposure to nano-sized ZnO on the airway inflammatory markers in healthy volunteers. To this end, we determined the influence of ZnO inhalation on the content of zinc and biomarkers (leukotriene B_4 (LTB_4), peptide leukotrienes (LTC_4/D_4/E_4), 8-iso-$PGF_{2\alpha}$, pH, and prostaglandin E_2 (PGE_2)) in exhaled breath condensate (EBC). Sixteen non-smoking subjects (8 females, 8 men) were exposed to filtered air (sham) or ZnO nanoparticles (0.5, 1.0, and 2.0 mg/m^3) for 4 h. EBC samples were collected according to specific study design. We found that the peptide leukotrienes were below the limit of quantification (LOQ) in all the EBC samples. ZnO exposure showed no detectable effect on any other parameters investigated when comparing the two groups. The content of Zn in EBC was unaffected by ZnO inhalation at any concentration used. Therefore, we conclude that the evaluation of Zn and biomarker content in EBC would not be a suitable way to assess the exposure to inhaled ZnO.

Keywords

Biomarkers · Exhaled breath condensate · Inhalation study · Nanoparticles · Zinc oxide

1 Introduction

Zinc and zinc compounds, like ZnO, occur in many industrial processes. Especially, galvanizing and welding workers are exposed to nano-sized ZnO particles. Inhalation of ZnO particles is known to cause systemic inflammatory responses named “metal fume fever” or “zinc fever” (Nemery 1990). Generally, there is a latency of a few hours until the onset of symptoms that resolve spontaneously in 48 h. The experimental inhalation studies investigating zinc-containing welding fumes have shown that the inflammatory effects occur at ZnO

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concentrations below 2.0 mg/m^3 (Brand et al. 2014; Hartmann et al. 2014). However, exposure to inhaled ZnO at 0.5 mg/m^3 for 2 h at rest results in no apparent effects (Beckett et al. 2005). Recently, we have reported flu-like symptoms, fever, and a concentration-dependent increase of inflammatory markers in blood after exposure to inhaled ZnO nanoparticles at or above 1 mg/m^3 (Monsé et al. 2018). In a further study in the same subjects, using the induced sputum, we detected reversible airway inflammation at a concentration of 0.5 mg/m^3 and higher, with no Zn concentration dependency (Monsé et al. 2019).

Exhaled breath condensate (EBC) offers a non-invasive matrix for assessing airway biomarkers and oxidative stress (Riddervold et al. 2012; Zanconato et al. 2004; Vaughan et al. 2003; Formanek et al. 2002; Shahid et al. 2002; Hunt et al. 2000; Jobsis et al. 1998). EBC, a fluid formed by cooling exhaled air, contains no cellular components. Thus, the evaluation is based on the metabolic products released by cells from the lungs or substances originating from the biochemical processes in the airway mucosa (Hoffmeyer et al. 2009). As EBC reflects the epithelial lining fluid, inhaled particles can also be analyzed. There is evidence that EBC sampling is suitable to assess pneumotoxic substances, like metals, providing a measure of exposure assessment (Hoffmeyer et al. 2011; Mutti and Corradi 2006). However, there is a paucity of human studies on the usefulness of EBC in the assessment of neutrophilic inflammation caused by acute inhalation of toxic substances. Hussain et al. (2012) have found an increase of nitrite in EBC in a diesel engine emission study. An increase in 8-isoprostane in the EBC has been found during exposure to ambient fine and ultrafine particles (Mills et al. 2008). Barregard et al. (2006) have found an increase in malondialdehyde, and Riddervold et al. (2012) have found a decrease in pH in the wood smoke studies. In contrast, Stockfelt et al. (2013) have failed to detect any changes in the EBC indices in another wood smoke study. Likewise, Hartmann et al. 2014 and Brand et al. 2013a, b have failed to detect any changes in the soluble EBC biomarkers in a study with welding fumes. The measurement of Zn in EBC after inhalation of Zn particle containing atmosphere has not yet been performed. Therefore, this study aimed to define the effects on the content of EBC inflammatory markers of short-term exposure to nano-sized ZnO. The overriding goal was to settle the issue of whether the EBC could be suitable for the estimation of the level of exposure to inhaled ZnO and its plausibly proinflammatory airway effects in humans.

2 Methods

2.1 Study Design and Participants

The detailed methods and experimental set-up including a graphical timeline have been recently described (Monsé et al. 2018). Briefly, potential volunteers were tested for their suitability to participate in the study during a baseline examination that included a questionnaire, medical examination, EBC, lung function test, exercise testing, and a collection of blood and induced sputum samples. To classify the volunteers as atopic or non-atopic, the serum was tested for specific IgE antibodies (sIgE) to ubiquitous allergens (sx1) using the ImmunoCAP 250 system (Phadiatop, Thermo Fisher Scientific, Uppsala, Sweden). A specific IgE concentration against sx1 of $\geq$ 0.35 kU/L was considered positive for atopy.

Participants had to be able to produce sputum according to the preset criteria (eosinophils <1%, epithelial cells <95%, and neutrophils being not dominant) to assess airway inflammation, to exclude asthmatics, and to ensure that the material originated from the lower airways. They should be not sensitized to ubiquitous allergens (sx1 negative). However, because healthy and non-smoking subjects can produce relatively poor amounts of induced sputum, we had to examine more than 60 subjects to single out 16 suitable ones. Out of these 16, 7 were sx1 positive (median 3.64 kU/L (range: 0.96–16.2 kU/L)) and were sensitized to seasonal (pollen) but not to perennial allergens. Thus, the study was performed out of the pollen season.

Table 1 Characteristics of the study population

Characteristics	All (n = 16)	Male (n = 8)	Female (n = 8)
Age (years)	26 (19–42)	28 (19–42)	24 (23–32)
Height (cm)	178 (155–191)	182 (176–191)	164 (155–182)
Weight (kg)	72 (51–104)	83 (61–104)	59 (51–91)
BMI (kg/m^2)	24 (19–29)	25 (20–29)	23 (19–27)
Total IgE (kU/L)	31 (2–329)	79 (2–208)	28 (20–329)
sIgE to sx1 (kU/L)	0.2 (0.1–16.2)	0.6 (0.1–4.1)	0.2 (0.1–16.2)
sIgE to sx1 $\geq$ 0.35 kU/L (n)	7	4	3

Data are medians (min-max). *BMI* body mass index, *sx1* an indicator of sensitization to environmental allergens

The recruitment of these volunteers was realized by advertising at universities and student residences. The subjects had no previous exposure to airborne zinc compounds. Standard baseline laboratory parameters were within normal ranges. Table 1 shows the subjects' characteristics. All the subjects were exposed for 4 h to ZnO particles with different concentrations (sham, 0.5, 1.0, and 2.0 mg/m^3 ZnO) in the exposure unit at the IPA Institute in Bochum, Germany (Monsé et al. 2012). They were examined during the 4-h exposure time at rest and periods of moderate physical exercise on a cycle ergometer set to 15 L/(min x m^2) corresponding to an individual workload of 30–96 W. Each 30-min rest was followed by a 30-min exercise, four times. Exposures were randomized and double-blinded, except for the exposure to 2.0 mg/m^3 ZnO, which was not blinded according to Institute Ethics Committee's requirement. Between each exposure with a different ZnO concentration, at least 2 weeks elapsed to minimize the carry-over effects. Examinations, including a sampling of EBC, were performed before, directly after, and approximately 24 h after each exposure. A final examination of each subject was performed about 2 weeks after the last exposure.

2.2 ZnO Particles

The synthesis of ZnO particles was based on the pyrolysis of atomized aqueous zinc formate solutions with a hydrogen-oxygen flame (Monsé et al. 2014). The investigation of homogeneity of the ZnO atmosphere was performed according to Pillar et al. (2016). Sham exposure (0 mg/m^3 ZnO) was performed using a flame generator operating with purified water without zinc salt (Monsé et al. 2014). This procedure ensured that the same concentration range of nitrogen oxides (NO_x) was present at all exposure levels which were generated as trace gases by the pyrolysis process (160–180 ppb each). Other measured trace gases are not expected to confound medical parameters in human exposure studies. The air exchange rate was set at 12 *per* hour (360 m^3/h) at a room temperature of 23.5 °C ± 0.3 °C and relative humidity of 47.0% ±1.7%.

The size of primary particles was 10 nm as determined under a scanning electron microscope (JSM-7500F, JEOL Ltd., Tokyo, Japan). Depending on the ZnO concentration, particles formed aggregates and agglomerates ranging from 48 nm (0.5 mg/m^3 ZnO) to 86 nm (2.0 mg/m^3 ZnO) as determined using a scanning mobility particle sizer (SMPS 3080, TSI Inc., Shoreview MN, equipped with a long differential mobility analyzer and a butanol condensation particle counter – model 3776, TSI Inc.). The particle size was comparable to that used in an emission study of galvanized materials with different welding techniques (Reisgen et al. 2012). An elementary analysis of the ZnO particles yielded a purity of 99.7% (Mikroanalytisches Labor Pascher, Remagen, Germany). The specific surface area was 20.2 m^2/g as determined using a BET device (Gemini VII 2390a, Micromeritics GmbH, Aachen, Germany).

2.3 Exhaled Breath Condensate (EBC)

Samples were collected at the baseline examination, then before exposure, directly after exposure, 24 h post-exposure, and at the final examination. The EBC was obtained using a Turbo DECCS device (Medivac, Parma, Italy) under standardized conditions (Hoffmeyer et al. 2015). By cooling the exhaled air for 15 min, a liquid phase was obtained. The non-volatile components of the exhaled air were collected by cooling at −5 °C. EBC pH was determined before and after argon fumigation with a glass electrode (Mettler Toledo, Giessen, Germany). For the detection of 8-iso-$PGF_{2\alpha}$, leukotriene B_4 (LTB_4), peptide leukotriene ($LTC_4/D_4/E_4$), and prostaglandin E_2 (PGE_2) in the supernatant aliquots, specific sandwich enzyme immunoassays kits were used (Assay Designs, Ann Arbor, CA). Details of the method and respective cross-reactivities have been previously reported (Hoffmeyer et al. 2009). The lower quantification limits were 6.1 pg/mL for 8-iso-$PGF_{2\alpha}$, 11.7 pg/mL for LTB_4, 78.1 pg/mL for $LTC_4/D_4/E_4$, and 7.8 pg/mL for PGE_2.

2.4 Analysis of Zinc in EBC

Biomonitoring was performed by determination of the Zn level in EBC. The EBC was collected in polyethylene vials. Before using the vials were intensively rinsed with 1 M nitric acid to avoid exogenous contamination. The aliquots were stored at 6 °C, provided that the analysis was carried out on the day of sampling. Otherwise, the sample was stored at −19 °C. Before analysis, the test material was homogenized and acidified with 20 µl of 65% nitric acid *per* 1 mL sample volume. The quantitative analysis was carried out using graphite furnace atomic absorption spectrometry (GF-AAS, ZEEnit 700, Analytik Jena, Germany) at 1800 °C with a wavelength of 213.9 nm. The injection volume was 20 µL. The calibration was carried out with a 0.3% nitric acid standard (aqueous) containing Zn in a range of 5.0 and 40.0 µg/L. Interfering influences of the biological matrix were largely eliminated using Zeeman background compensation. For each sample series, 0.3% nitric acid was used as a reagent blank instead of EBC. The limit of quantification (LOQ) was 1.0 µg/L Zn. Recovery rates were between 90% and 110% at a Zn concentration of 20 µg/L.

2.5 Data Analysis

Descriptive analysis was performed for each variable stratified by exposure (sham, 0.5, 1.0, and 2.0 mg/m^3 ZnO) and time of measurement (before, directly after, and 24 h after exposure). Characteristics of subjects were expressed as medians, 25–75% quantiles, and min-max values. Graphical representations were illustrated with boxplots using GraphPad Prism v5.04 software (San Diego, CA). The effects were compared between the data sampled before, directly after, and 24 h after exposure. Additionally, the effects after sham exposure were compared to those after ZnO exposures. Group comparisons were done using a paired *t*-test for normal or log-normal distributed variables.

3 Results

In all the EBC samples, the concentrations of the peptide leukotrienes ($LTC_4/D_4/E_4$) were below the LOQ. The content of Zn in EBC was unaffected by ZnO inhalation at any concentration as it remained within the fluctuation range of measurements. ZnO exposures showed no detectable effect on the EBC indices LTB_4 (7% < LOQ), 8-iso-$PGF_{2\alpha}$ (15% < LOQ), pH, and PGE_2 (63% < LOQ) in the inter-group comparisons (Fig. 1; Table 2).

4 Discussion

Experimental inhalation studies in humans with nanoparticles which use multiple concentration

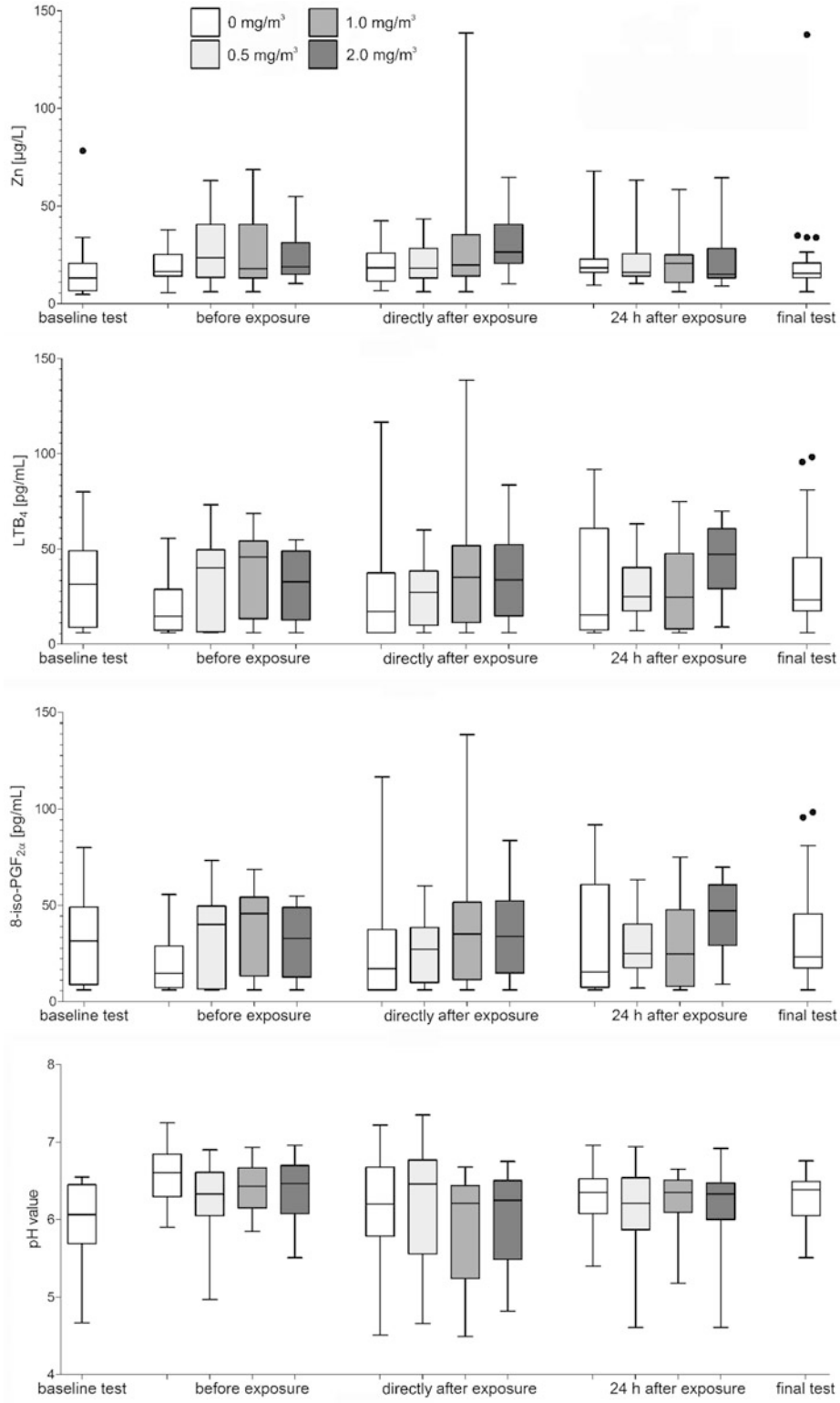

Fig. 1 Total levels of Zn, LTB_4, 8-iso-$PGF_{2\alpha}$, and pH according to ZnO concentration and time points. Outliers are defined as values above the median + 1.5 x interquartile range or values below the median − 1.5 x interquartile range

Table 2 Effects of zinc oxide (ZnO) exposure assessed in the exhaled breath condensate (EBC) (n = 16)

	ZnO (mg/m^3)	Before exposure	Directly after exposure	24 h after exposure
Zn (µg/L)	0	16.9 (11.1–39.9)	14.2 (7.9–42.3)	12.7 (8.2–39.1)
	0.5	20.9 (12.1–44.7)	21.0 (9.8–48.9)	15.4 (8.7–24.1)
	1	13.1 (4.1–27.2)	19.6 (5.3–36.7)	18.9 (10.5–26.7)
	2	17.9 (5.0–39.9)	25.5 (17.4–43.7)	13.4 (7.7–67.9)
LTB_4 (pg/mL)	0	1325 (930–1700)	1400 (780–1800)	1300 (500–1600)
	0.5	1300 (550–1600)	1400 (900–1800)	1400 (980–1900)
	1	1275 (750–1800)	1350 (1100–1750)	1300 (700–2000)
	2	1375 (800–1800)	1300 (800–1500)	1275 (700–1750)
8-iso $PGF_{2\alpha}$ (pg/mL)	0	14.8 (<6.1–55.6)	17.1 (<6.1–116.6)	15.4 (<6.1–91.8)
	0.5	40.1 (<6.1–73.3)	27.2 (<6.1–60.0)	25.0 (7.1–63.2)
	1	45.7 (<6.1–68.6)	35.1 (<6.1–138.6)	24.7 (<6.1–74.9)
	2	32.8 (<6.1–54.8)	32.92 (<6.1–83.6)	47.12 (9.1–69.8)
pH	0	6.5 (5.9–6.9)	6.1 (4.5–7.0)	6.4 (5.4–7.0)
	0.5	6.2 (4.9–6.7)	6.5 (4.6–7.3)	6.2 (4.6–6.9)
	1	6.4 (5.8–7.0)	6.2 (4.5–6.6)	6.2 (5.2–6.6)
	2	6.3 (5.5–7.1)	6.2 (4.7–6.7)	6.2 (4.8–7.0)
PGE_2 (pg/mL)	0	<7.8 (<7.8–13.4)	<7.8 (<7.8–13.2)	<7.8 (<7.8–12.4)
	0.5	8.2 (<7.8–24.8)	8.0 (<7.8–13.1)	8.3 (<7.8–20.8)
	1	<7.8 (<7.8–15.1)	<7.8 (<7.8–21.9)	<7.8 (<7.8–9.2)
	2	<7.8 (<7.8–24.1)	<7.8 (<7.8–26.0)	<7.8 (<7.8–19.8)

Data are medians (min-max)

steps to describe a concentration-response relationship are sparse. The present study is, to our knowledge, the first inhalation study that examined, with a high degree of methodological quality, several indices in induced sputum and EBC in a multi-concentration design of 0, 0.5, 1.0, and 2.0 mg/m^3 ZnO. However, we could not detect significant concentration-dependent effects on the EBC indices of exposure to ZnO inhalation up to 2.0 mg/m^3.

There are no comparable studies on the effects of ZnO particles on EBC parameters. However, previous studies demonstrate a concentration-dependent response in systemic ZnO effects. A key result of a study by Monsé et al. (2018) has been an increase in acute phase proteins (C-reactive protein (CRP) and serum amyloid A (SAA)) and neutrophil count in the blood, followed by an increase in body temperature and the occurrence of flu-like symptoms at and above 1 mg/m^3 ZnO. A further result is a demonstration of an inflammatory airway response in induced sputum, although not concentration-dependent at 0.5 mg/m^3 ZnO and higher. That study also demonstrates that FeNO and lung function parameters are not affected by ZnO exposures. In another study, some effects of exposure to nano-sized ZnO particles have been noticed in induced sputum concerning the levels of neutrophils, interleukin-8, interleukin-6, matrix metalloproteinase-9, and tissue inhibitors of metalloproteinase-1 (Monsé et al. 2019). All systemic and local effects were reversible about 2 weeks after the last ZnO exposure.

Experimental inhalation studies are complex, cumbersome, and cost-intensive. Therefore, such studies usually include 10–20 participants (Miller et al. 2017; Mills et al. 2006; Kuschner et al. 1997). The small number of participants is a problem if no effects are observed, because according to the power analysis, much higher numbers of test persons are required for indices with a high variance to avoid significant errors, particularly concerning local endpoints. Discouragingly high variances of the indices investigated in the present study made it irrational to employ the multivariate models for the statistical elaboration as such models might be unreliable due to a small number of participants. Therefore, we consider the number of 16 subjects in this study a

limitation, but studies with a much higher number of subjects cannot be conducted with reasonable effort. The fact that no dose-dependent effects were observed reinforces the interpretation that this part of the study is indeed a negative outcome. Another limitation of EBC analysis for airway inflammation markers is a large dilution of a sample, resulting in low concentrations of constituents (Dodig and Čepelak 2013). The $LTC_4/D_4/E_4$ and PGE_2 biomarkers were below the LOQ, a clear limitation of EBC analysis in this study. A few effects that could be measured were unaffected by ZnO exposures. While some other studies have shown alterations in EBC indices after inhalation exposure to hazardous substances other than zinc, the studies by Brand et al. (2013a, b) and Hartmann et al. (2014), akin to the present study, have shown the results remaining below the EBC-relevant effect values.

In summary, no significant changes in soluble inflammatory markers were detected in EBC in response to inhalation exposure to successive concentrations of 0, 0.5, 1.0, and 2.0 mg/m^3 ZnO. The total level of Zn in EBC remained unaffected either. Thus, we may reasonably conclude that the determination of the EBC indices investigated in this study offers no advantage for assessing the effect of zinc exposure up to 2.0 mg/m^3.

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Conflicts of Interest The authors declare no conflicts of interest concerning this article.

Ethical Approval All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Ruhr University Bochum in Germany.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

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Cognitive Function After Lung Transplantation

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Abstract

Cognitive functioning after transplantation, which could influence medication compliance and independence, has not been well studied. This study investigated cognitive impairment after lung transplantation. Patients undergoing bilateral transplant between March 2013 and October 2015 underwent comprehensive neuropsychological assessment at 60.1 ± 44.1 months post-transplantation: verbal memory (Auditory-Verbal Learning Test, digit span forward), visual memory (Corsi Block-Tapping Test forward, Benton Visual Retention Test), concentration/speed of processing/attention (D2 Test of Attention, Trail Making Test (TMT) A, Grooved Pegboard), and executive functioning (TMT B, Stroop Color-Word Test, semantic and phonematic verbal fluency, digit span backward, Corsi Block-Tapping Test backward). Mean scores were compared with a normative dataset using a one-sample *t*-test. A cognitive domain was judged impaired if the score on two or more domain-specific tests was greater than one standard deviation below the normative dataset age range mean. Of 124 lung transplant recipients (51% male, 54.3 ± 9.0 years), 70% showed cognitive impairment in one or more domains. Executive function was most often impaired (78% of recipients not within the age range)

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followed by verbal memory impairment (72% not within the age range). Cognitive function reductions were largely independent of age, gender, education, immunosuppressive medications, and time since transplantation. The findings show that cognitive impairment is common after lung transplantation and should be subject to rehabilitation and psychological resilience strategies.

Keywords

Cognition · Executive functions · Lung transplantation · Cognitive impairment · Memory · Neuropsychological assessment

1 Introduction

For patients with end-stage lung disease, lung transplantation is an established intervention that improves the quality of life and mortality (Orens and Garrity Jr 2009; Arcasoy and Kotloff 1999). The International Society for Heart and Lung Transplantation registered 60,107 adult lung transplantations from January 1995 to June 2016, representing 75% of the worldwide thoracic transplant activity (Chambers et al. 2017). Not surprisingly, advanced lung disease is associated with diminished resilience and reduced quality of life in patients awaiting lung transplantation. These patients often show cognitive impairment (Yohannes et al. 2017), possibly due to hypoxia and hypercapnia associated with advanced lung disease (Parekh et al. 2005). There is evidence of a further decline in cognitive functioning after lung transplantation in some recipients (Smith et al. 2014), while other studies do not show striking differences in cognitive impairment before and after transplantation or show a slight improvement in some recipients (Cohen et al. 2014; Hoffman et al. 2012).

Studies examining cognitive functioning after lung transplantation are scarce and often do not differentiate between cognitive domains. Most studies examine neuropsychological deficits in end-stage lung disease patients before transplantation (Yohannes et al. 2017). It seems important to precisely quantify post-transplantation cognitive impairment because it has implications regarding medication compliance and overall independence. Furthermore, it is important to know what to expect post-transplant and to implement strategies to compensate and rehabilitate cognitive deficits, but strategies may differ depending on the affected cognitive domain(s).

This study used a comprehensive neuropsychological assessment to assess cognitive functioning in four domains (verbal memory, visual memory, concentration/speed of processing/attention, and executive functioning) in lung transplant recipients compared with a normative dataset and examined the distribution of impaired domains.

2 Methods

2.1 Study Design and Patients

A total of 124 patients (mean age 54.3 ± 9.1 years; 51% men), who underwent bilateral lung transplantation between March 2013 and October 2015, were included in the study. The most common indication for transplantation was the chronic obstructive pulmonary disease, more than one-third of patients had chronic kidney disease, and a minority had anxiety or depression (Table 1). The interval between lung transplantation and neuropsychological assessment ranged in individual patients from 1 to 264 months (mean 60.1 ± 44.1 months).

2.2 Neuropsychological Assessments

Verbal memory was tested using a German version of the Auditory-Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest) consisting of the immediate word span, total acquisition, immediate retroactive interference, delayed recall, and recognition (Helmstaedter et al. 2001) and the digit span forward of the

Table 1 Sociodemographic and clinical characteristics of the study patients (n = 124)

Age, years	54.3 ± 9.1
Male, n (%)	63 (51)
Education, years	12.4 ± 2.3
Pulmonary diagnosis, n (%)	
COPD	48 (39)
Idiopathic pulmonary fibrosis	29 (23)
Cystic fibrosis	13 (10)
Alpha 1-antitrypsin deficiency	13 (10)
Pulmonary arterial hypertension	3 (3)
Sarcoidosis	1 (1)
Others[a]	17 (14)
Immunosuppressive medication, n (%)	
Tacrolimus	64 (51)
Cyclosporine	36 (29)
Sirolimus	21 (17)
Tacrolimus + sirolimus	2 (2)
Cyclosporine + sirolimus	1 (1)
Coexisting conditions, n (%)	
Diabetes	20 (16)
Hypertension	48 (39)
Chronic kidney disease	77 (62)
Time after transplantation, months	
Mean ± SD	60.1 ± 44.1
Median (interquartile range)	58 (21–90)
Obesity (BMI >30 kg/m^2), n (%)	17 (14)
Anxiety score[b]	5.0 ± 3.5
Probable presence of anxiety disorder, n (%)	9 (7)
Depression score[b]	3.0 ± 3.0
Probable presence of depression, n (%)	4 (3)

Data are expressed as means ±SD unless otherwise specified; *BMI* body mass index, *COPD* chronic obstructive pulmonary disease; [a]others include hypersensitivity pneumonitis (n = 5), bronchiectasis (n = 3), Langerhans histiocytosis (n = 3), lymphangioleiomyomatosis (n = 2), progressive systemic scleroderma (n = 1), lupus erythematosus (n = 1), sarcoidosis (n = 1), toxic bronchiolitis (n = 1); [b]Hospital Anxiety and Depression Scale (range: 0–21 points, normal range: 0–7 points, 11 points or higher indicates a likely mood disorder)

Wechsler Memory Scale to assess verbal short-term memory (Härting et al. 2000). Short-term visual memory was tested using the Corsi Block-Tapping Test of the Wechsler Memory Scale (Härting et al. 2000), and visual learning was assessed using the Benton Visual Retention Test (Benton Sivan and Spreed 2009).

The neuropsychological attention and concentration ability were assessed from the processing speed and accuracy measured with the D2 Test of Attention (Brickenkamp 2002). The Grooved Pegboard Test was used to measure psychometric speed and coordination (Klove 1963). The Trail Making Test (TMT) A (Reitan 1955) was used to assess the speed of processing. TMT B was used to assess cognitive flexibility and attention. The scores of TMT tests were referenced to the normative data reported by Tombaugh (2004). The executive functions of mental control and inhibition were assessed using the Stroop Color-Word Test (Bäumler 1985). The manual for this test does not provide the median values for the normative dataset, providing T-values of performance instead. Thus, we transformed the median values into T-values and compared these with the corresponding normative T-values. To assess executive divergent thinking, we used two verbal fluency tests. First, participants were asked

to come up with as many words as possible starting with the letter "S" and then to name as many first names as possible, both with a 2-min time limit. The digit span backward and the Corsi Block-Tapping Test of the Wechsler Memory Scale were used to assess verbal and visual working memory, respectively (Härting et al. 2000).

2.3 Assessment of Covariates

Education was classified by the International Standard Classification of Education as total years of formal education, combining school and vocational training (UNESCO 1997). Immunosuppressive medication concerned agents that may have differential impacts on cognitive function. Some existing data suggest that intake of calcineurin inhibitors (e.g., cyclosporine or tacrolimus) is associated with reduced cognitive function, although results are not consistent (Kahl et al. 2017; Scherwath et al. 2013; Martínez-Sanchis et al. 2011; Griva et al. 2004; Padovan et al. 1998). Conversely, sirolimus is reported to have protective effects on cognition and synaptic plasticity in rodents (Fu et al. 2017; Lin et al. 2017). Thus, sirolimus was the reference agent in our analyses. Coexisting conditions were determined from medical records. Obesity was defined as a body mass index (BMI) >30 kg/m^2. The Hospital Anxiety and Depression Scale was used to assess anxiety and depression symptoms. The participant answers seven items of either type of symptoms, where a score of 8–10 out of the possible 21 is indicative of a disorder (Snaith and Zigmond 1986).

A cognitive test was rated as impaired performance if the score was >1SD below the age norm of the normative dataset. A cognitive domain was rated as impaired when two or more domains scored >1SD below the mean of the age-group.

2.4 Statistical Analysis

Age groups for the comparison of neuropsychological tests were based on the age range in the normative datasets for the corresponding test. The mean scores of tests for lung transplant recipients were compared with the normative dataset using a one-sample *t*-test with the mean of the normative dataset as the critical value. After Bonferroni correction, a p-value $\leq$0.0011 was considered statistically significant. The mean between-group differences with 95% confidence intervals (CI) were reported. Lung transplant recipients who performed 1SD below the age norm of the normative dataset for each neuropsychological test and in two or more tests for each cognitive domain were identified and the number and pattern of impaired domains determined. Binary logistic regression models (impaired vs. non-impaired) were constructed for each cognitive domain to examine the association of age (linear, per year), sex (male as reference), education (linear, per year), immunosuppressive medication (intake of cyclosporine/tacrolimus vs. sirolimus as reference), and time after transplantation (linear, per year) with cognitive performance, reported as odds ratio (OR) with 95% CI. Both unadjusted and adjusted models for statistically significant unadjusted results were presented. Covariates for the adjustment were age, sex, education, immunosuppressive medication, and/or time after lung transplantation depending on the model. All analyses were conducted using PASW Statistics v24 (SPSS Inc.; Chicago, 2016).

3 Results

3.1 Verbal Memory

Significant differences between lung transplant recipients aged $\geq$55 years and the normative dataset were only seen for immediate retroactive interference, delayed recall, and recognition minus false-positive answers (all $p < 0.001$) (Table 2). Overall, 35 (28%) recipients showed verbal memory performance within the normal age range; 89 (72%) performed >1SD below the age norm in at least 1 verbal memory test, and 52 (42%) showed impaired performance in 2 or more verbal memory tests. The probability of having verbal memory impairment was independent of age (OR 1.02 (95% CI 0.98–1.06) *per*

Table 2 Verbal and visual memories in lung transplant patients compared with the normative dataset

		Lung transplant patients (n = 124)		Comparison with normative dataset[b]			
	Age[a]	n	Mean ± SD	Mean difference[c]	95% CI	p-value	Performance > 1SD below age norm, n (%)
Verbal memory							
Immediate word span[d]	≤49	36	6.53 ± 1.98	−0.22	−0.89, 0.45	0.510	16 (13)
	≥50	88	5.80 ± 1.67	0.21	−0.15, 0.56	0.250	
Total acquisition[e]	≤49	36	50.81 ± 8.86	−1.58	−4.58, 1.41	0.290	21 (17)
	≥50	88	46.17 ± 9.26	−1.52	−3.48, 0.44	0.130	
Immediate retroactive interference[f]	≤49	36	2.00 ± 1.99	0.56	−0.11, 1.23	0.100	37 (30)
	≥50	87	2.66 ± 1.92	0.94	0.53, 1.34	**<0.001**	
Delayed recall[g]	≤49	35	10.74 ± 2.80	0.47	−0.16, 1.10	0.160	30 (24)
	≥50	88	9.92 ± 3.10	−1.47	−2.13, −0.82	**<0.001**	
Recognition[h]	≤49	35	11.09 ± 6.19	−2.71	−4.84, −0.59	0.014	21 (17)
	≥50	87	12.44 ± 4.40	−0.83	−1.77, 0.10	0.080	
Recognition minus false-positive answers[i]	≤49	35	10.11 ± 5.98	−2.65	−4.70, −0.59	0.013	39 (31)
	≥50	87	10.26 ± 4.90	−2.06	−3.10, −1.01	**<0.001**	
Verbal short-term memory[j]	≤54	57	7.44 ± 2.08	−0.49	−1.04, 0.06	0.080	27 (22)
	≥55	67	7.00 ± 2.22	−0.19	−0.73, 0.36	0.500	
Visual memory							
Visual short-term memory[k]	≤54	57	8.18 ± 1.30	0.25	−0.10, 0.59	0.080	35 (28)
	≥55	67	7.22 ± 1.52	−0.68	−1.05, −0.31	0.001	
Visual learning[l]	≤39	7	7.86 ± 1.57	−0.11	−1.57, 1.34	0.860	24 (19)
	40–49	27	5.96 ± 1.85	−0.31	−1.04, 0.42	0.400	
	50–59	39	6.18 ± 2.10	−0.34	−1.02, 0.34	0.320	
	≥60	47	6.28 ± 1.74	0.52	0.01, 1.03	0.048	

CI, confidence interval; *SD,* standard deviation

[a]Age (years) group was selected based on the age range in the normative dataset

[b]Normative data were derived from the manual of the corresponding test (for references see methods section)

[c]Comparisons were performed with a one-sample *t*-test, with the mean of the normative dataset as a critical value (after Bonferonni correction the p-values must be ≤0.0011 to define statistical significance)

[d]Auditory-Verbal Learning Test, recall of words in the trail I of list A (range: 2–10, higher scores indicate better performance)

[e]Auditory-Verbal Learning Test, the total number of recalled words in the five-trial presentation (range: 10–68, higher scores indicate better performance)

[f]Auditory-Verbal Learning Test, words recalled in trial V minus words recalled after the interference of list B (range: minus 2-10, higher scores indicate lower performance); data unavailable for one participant

[g]Auditory-Verbal Learning Test, delayed recall of list A (range: 2–15, higher scores indicate better performance); data unavailable for one participant

[h]Auditory-Verbal Learning Test, recognition of list A (range: 0–15, higher scores indicate better performance); data unavailable for two participants

[i]Auditory-Verbal Learning Test, recognition of list A minus false-positive recognition of words that were not the words in list A (range: minus 1-15, higher scores indicate better performance), data unavailable for two participants

[j]Wechsler Memory Scale, digit span forward (range: 2–12, higher scores indicate better performance)

[k]Corsi Block-Tapping Test of the Wechsler Memory Scale, forward span (range: 4–13, higher scores indicate better performance)

[l]Benton Visual Retention Test, number of correct drawings (range: 0–9, higher scores indicate better performance), data not available for four participants

1-year increase), sex (OR 1.23 (0.60–2.52) for females vs. males), time after lung transplantation (OR 0.89 (0.80–1.00) *per* 1-year increase), and immunosuppressive medication (OR 1.18 (0.45–3.09) for cyclosporine/tacrolimus vs. sirolimus). The risk of verbal memory impairment was significantly increased in patients with higher education levels (adjusted OR 1.24 (1.01–1.53)) per 1-year increase.

3.2 Visual Memory

The only significant difference between lung transplant recipients and the normative dataset was for visual short-term memory in patients aged ≥55 years ($p < 0.001$) (Table 2). Fifty-one transplant recipients (41%) performed >1SD below the age norm in at least one visual memory test, while eight showed impaired performance in two or more visual memory tests. The probability of having visual memory impairment was independent of age (OR 0.99 (0.96–1.03) *per* 1-year increase), sex (OR 0.68 (0.33–1.39) for females vs. males), and education (OR 0.99 (0.83–1.19) *per* 1-year increase). The intake of cyclosporine/tacrolimus was less likely to be associated with visual memory impairment (OR 0.32 (0.06–1.62) vs. sirolimus)). The adjusted OR for impairment in the visual memory domain was significantly associated with time since transplantation (OR 1.31 (1.07–1.60) *per* 1-year increase).

3.3 Concentration, Speed of Processing, and Attention

Lung transplant recipients performed significantly worse than the normative dataset only in the concentration task (Table 3). Seventy-four recipients (60%) performed >1SD below the age norm in at least one concentration, speed of processing, and attention test, and 35 (28%) showed impaired performance in two or more of these tests. The probability of having impaired concentration, speed of processing, and attention was independent of age (OR 1.04 (0.99–1.09), *per* 1-year increase), sex (OR 0.64 (0.29–1.41) for females vs. males), education (OR 1.07 (0.88–1.30) *per* 1-year increase), and immunosuppressive medication (OR 0.57 (0.21–1.53) for cyclosporine/tacrolimus vs. sirolimus). The risk of impairment in this domain increased significantly as the duration after lung transplantation increased in the unadjusted analysis (OR 1.12 (1.00–1.24) *per* 1-year increase), but not after adjustment for age, sex, education, and duration after lung transplantation (OR 1.08 (0.96–1.21)).

3.4 Executive Functioning

Older lung transplantation recipients showed significantly worse performances in cognitive flexibility, verbal fluency, and visual working memory (Table 4). Only did 27 (22%) recipients show executive functioning within the normal age range; 97 (78%) performed >1SD below the age norm in at least 1 test, and 61 (49%) showed impaired performance in two or more executive functioning tests. The likelihood of having impaired executive functioning was higher in older recipients in both the unadjusted (OR 1.05 (1.01–1.10) *per* 1-year increase) and adjusted (OR 1.05 (1.01–1.10) *per* 1-year increase) analysis and with a longer duration after lung transplantation in the unadjusted (OR 1.12 (1.01–1.24) *per* 1-year increase) but not the adjusted analysis (OR 1.10 (0.99–1.23) *per* 1-year increase). Education (OR 0.97 (0.81–1.16) *per* 1-year increase), sex (OR 1.29 (0.64–2.63) for females vs. males), and immunosuppressive medication (OR 1.02 (0.40–2.60) for cyclosporine/tacrolimus vs. sirolimus) had no significant influence on the likelihood of having impaired executive function.

3.5 Overall Cognitive Impairment

No impairment in any domain was seen in almost one-third of patients (Table 5). Just over one-third showed impairment in one domain, with verbal memory and executive functioning most often

Table 3 Concentration, speed of processing, and attention in lung transplant patients compared with the normative dataset

		Lung transplant patients (n = 124)		Comparison with normative dataset[b]			
	Age[a]	n	Mean ± SD	Mean difference[c]	95% CI	p-value	Performance > 1 SD below age norm, n (%)
Concentration[d]	≤39	8	155.75 ± 15.30	−27.05	−39.84, −14.26	0.002	55 (44)
	≥40	111	117.75 ± 37.52	−39.75	−46.81, −32.70	**<0.001**	
Speed of processing/ attention[e]	≤44	22	25.59 ± 8.02	−0.88	−4.43, 2.67	0.61	22 (18)
	45–59	54	32.94 ± 10.87	0.34	−2.62, 3.31	0.82	
	≥60	48	37.04 ± 10.39	1.45	−1.57, 4.47	0.34	
General slowing[f] (dominant hand)	≤39	8	62.88 ± 10.11	−0.31	−8.75, 8.14	0.93	20 (16)
	40–49	27	66.48 ± 12.83	2.98	−2.09, 8.06	0.24	
	50–59	40	71.83 ± 15.04	3.75	−1.09, 8.54	0.13	
	≥60	48	81.40 ± 21.39	−1.30	−7.52, 4.91	0.68	
General slowing[g] (non-dominant hand)	≤39	8	64.38 ± 5.90	−3.86	−8.76, 1.08	0.11	27 (22)
	40–49	26	73.23 ± 13.03	4.18	−1.10, 9.46	0.12	
	50–59	40	81.38 ± 23.62	6.68	−0.88, 14.23	0.08	
	≥60	48	88.75 ± 21.47	0.80	−5.43, 7.03	0.80	

CI confidence interval, *SD* standard deviation

[a]Age (years) group was selected based on the age range in the normative dataset

[b]Normative data derived from the manual of the corresponding test (for references see methods section)

[c]Comparisons calculated using a one-sample *t*-test with the mean of the normative dataset as a critical value (after Bonferonni correction the p-values must be ≤0.0011 to define statistical significance)

[d]D2 Test of Attention, number of correct detected "ds" with two marks minus the number of false-positive detections (range: 9–212, higher scores indicate better performance), data unavailable for five participants

[e]Trail Making Test A, time in seconds (range: 14–64, higher scores indicate lower performance)

[f]Grooved Pegboard, time in seconds needed to complete the task with the dominant hand (range: 47–146, higher scores indicate lower performance), data unavailable for one participant

[g]Grooved Pegboard, time in seconds needed to complete the task with the non-dominant hand (range: 56–200, higher scores indicate lower performance), data unavailable for two participants

affected. When two domains were impaired, all recipients had impairment in executive functioning. With impairment of three domains, lung transplant recipients most often showed impairment in concentration/speed of processing/attention, followed by verbal memory and executive functioning.

4 Discussion

This observational cohort study found that most lung transplant recipients have cognitive impairment in at least one domain. The domain most likely to be affected was executive functioning, with less than one-quarter of recipients performing within their age range on these tests. Verbal memory was the next affected domain and was age-appropriate in only 28% of lung transplant recipients. These findings are consistent with some of the scarce studies showing cognitive impairment after lung transplantation. However, there are only two studies that have examined performance in different cognitive domains after lung transplantation. Hoffman et al. (2012) have used verbal memory and executive functioning tests akin to those used in the present study. Of the 49 patients who completed assessments, the proportion of patients who scored >1SD below normative data was 35% in the digit span (vs. 22% in our cohort), 20% in the TMT A (vs. 18%), 12% in TMT B (vs. 47%), 31% in

Table 4 Executive functioning in lung transplant patients compared with the normative dataset

Executive functioning	Age[a]	Lung transplant patients (n = 124)		Comparison with normative dataset[b]			
		n	Mean ± SD	Mean difference[c]	95% CI	p-value	Performance > 1 SD below age norm, n (%)
Cognitive flexibility[d]	≤44	22	67.82 ± 35.78	13.25	−2.61, 29.11	0.100	58 (47)
	45–59	54	97.85 ± 46.56	29.07	16.36, 41.78	**<0.001**	
	≥60	48	121.60 ± 62.93	42.48	24.21, 60.76	**<0.001**	
Inhibition[e]	≤39	8	56.13 ± 5.36	−0.58	−5.05, 3.90	0.770	23 (19)
	40–59	65	51.22 ± 7.93	−1.38	−3.35, 0.58	0.160	
	≥60	46	49.48 ± 6.94	−3.32	−5.38, −1.26	0.002	
Verbal fluency (phonematic category)[f]	≤50	38	18.76 ± 5.26	−2.12	−3.85, −0.39	0.018	34 (27)
	≥51	80	18.69 ± 7.0	−1.26	−2.82, 0.30	0.110	
Verbal fluency (semantic category)[g]	≤50	39	34.41 ± 12.8	−1.05	−5.20, 3.10	0.270	39 (31)
	≥51	80	32.29 ± 8.55	−4.40	−6.31, −2.50	**0.001**	
Verbal working memory[h]	≤54	57	6.40 ± 1.82	−0.50	−0.98, −0.01	0.044	34 (27)
	≥55	67	5.72 ± 2.22	−0.55	−1.10, −0.01	0.045	
Visual working memory[i]	≤54	57	7.56 ± 1.70	−0.67	−1.12, −0.22	0.004	34 (27)
	≥55	67	6.46 ± 1.71	−0.74	−1.15, −0.32	**0.001**	

CI, confidence interval; *SD,* standard deviation

[a]Age (years) group was selected based on the age range in the normative dataset

[b]Normative data derived from the manual of the corresponding test (for references, see methods section)

[c]Comparisons calculated using a one-sample t-test with the mean of the normative dataset as a critical value (after Bonferonni correction the p-values must be ≤0.0011 to define statistical significance)

[d]Trail Making Test B, time in seconds, (range: 35–300, higher scores indicate lower performance)

[e]Stroop Color Word Test, the median time needed to complete the three interference sheets was transformed into T-values and compared with the T-values of the normative dataset (range of T values: 30–69, higher scores indicate better performance), data unavailable for five participants

[f]Verbal fluency: phonematic category "S" (range: 0–39, higher scores indicate better performance), data unavailable for five participants

[g]Verbal fluency: semantic category "first names" (range: 0–71, higher scores indicate better performance), data unavailable for five participants

[h]Wechsler Memory Scale, digit span backward (range: 2–11, higher scores indicate better performance)

[i]Corsi Block-Tapping Test of the Wechsler Memory Scale, backward span (range: 3–11, higher scores indicate better performance)

verbal fluency (vs. 32%), and 22% in the Stroop Test (vs. 19%). Smith et al. (2014) have used a composite measure including the Repeatable Battery for the Assessment of Neuropsychological Status, the Montreal Cognitive Assessment Battery, and the TMT A and B. They found neurocognitive performance to initially worsen among non-cystic fibrosis lung transplant recipients and then improve over time, with 57% of recipients showing cognitive impairment 3 months after transplantation. These findings cannot be directly compared with ours because of the different measures used. Akin to the present findings, both previous studies show impairment primarily in executive functioning and verbal memory. However, in contrast to the present study, previous trials did not examine visual memory and included only a few attention tests.

It is possible that executive functioning and verbal memory are the most impaired post-transplant cognitive function domains because all recipients had end-stage lung disease before transplantation. End-stage lung disease decreases blood oxygen levels (hypoxia) and increases blood carbon dioxide levels (hypercapnia) (Parekh et al. 2005; Neubauer 2001; Stuss et al.

Table 5 Number of impaired and affected cognitive function domains in lung transplant recipients

Number of impaired domains[a]	n (%)	Affected domain[b]	% Patients
0	37 (30)		
1	42 (34)	Verbal memory	45
		Visual memory	0
		Concentration, speed of processing, attention	14
		Executive functioning	41
2	26 (21)	Verbal memory	58
		Visual memory	4
		Concentration, speed of processing, attention	38
		Executive functioning	100
3	14 (11)	Verbal memory	93
		Visual memory	14
		Concentration, speed of processing, attention	100
		Executive functioning	93
4	5 (4)	Verbal memory	100
		Visual memory	100
		Concentration, speed of processing, attention	100
		Executive functioning	100

Data are presented as number (%) or % patients unless otherwise indicated

[a]Impaired domain was defined as cognitive performance in at least two domain-specific neuropsychological tests of >1SD below the age mean

[b]Affected domains were those with at least two neuropsychological test results >1SD below the age mean

1997). Executive functions and verbal memory are associated with distinct neural correlates located in the prefrontal cortices and the left hippocampus, respectively (Henke 2010), the areas particularly vulnerable to hypoxia (Gale and Hopkins 2004). The present findings also are consistent with studies in patients with obstructive sleep apnea, which is characterized by repetitive episodes of partial or complete upper airway obstruction associated with various degrees of hypoxia and hypercapnia and is associated with pronounced impairment in executive functioning and long-term memory (Bucks et al. 2013; Beebe et al. 2003). Neurodegenerative processes caused by hypoxia and hypercapnia might be reversible only to a minimal extent (Zlokovic 2011). Thus, cognitive deficits persist after transplantation and may slightly improve over time, due likely to increased quality of life or reduced depression and anxiety after transplantation (Thabut and Mal 2017).

The present findings have implications for post-transplant management of transplant recipients. Cognitive impairment may compromise the recipient's ability to comply with complex post-transplant medical requirements, particularly concerning the immunosuppressive medications increases, which increases the risk of graft loss and death. It could be helpful to assess recipients before and after transplantation to implement individualized strategies to compensate for and rehabilitate cognitive impairment. The strategies differ depending on the affected cognitive domain, highlighting the importance of a comprehensive cognitive function assessment across a range of domains.

Mechanisms underlying cognitive decline after organ transplantation remain unclear (Cohen et al. 2014; Smith et al. 2014; Diamond and Mikkelsen 2004). They might include perioperative factors (e.g., allograft ischemic time, primary graft dysfunction, time on mechanical ventilation, intraoperative hypoxia, micro-emboli, length of intensive care unit stay), and postoperative factors (e.g., delirium, physical function after transplantation, acute rejection, and immunosuppressive medication). Due to the cross-sectional design of the present study, we cannot draw firm conclusions about cognitive decline compared with pre-transplant cognitive status.

This study has some limitations. Cognitive function was assessed after lung transplantation only. Therefore, the extent of pre-transplant cognitive impairment, if any, was unclear, making it difficult to elucidate post-transplant changes in cognitive function. Further, the cognitive function of lung transplant recipients was compared with normative data for the neuropsychological tests used. It would have been better to use data from age- and education-matched non-transplant controls, which might help clarify the degree of cognitive impairment specifically attributable to transplantation, or to compare lung transplant recipients with matched controls who underwent transplantation of a different organ with comparable surgery duration and postoperative hospitalization. That would have also allowed controlling for cardiovascular risk factors. However, the classification of cognitive impairment is usually based on normative data. We were unable to compare cognitive function with information about perioperative or postoperative risk factors and could not determine whether cognitive impairment depended on such factors. However, regression analysis showed no relation of cognitive impairment to the time lapse in most instances. A key advantage of our study was a large cohort of lung transplant recipients that were prospectively evaluated using a comprehensive neuropsychological assessment. The sample will be followed longitudinally to examine further changes in cognition after transplantation.

We conclude that cognitive impairment is common among lung transplant recipients. It is suggested that cognitive function should be assessed across a range of domains to help develop personalized rehabilitation and psychological resilience strategies after lung transplantation.

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Conflicts of Interest The authors of this manuscript have no conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of the University Duisburg-Essen in Germany.

Informed Consent All patients gave written informed consent to participate in the study.

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