MINI-REVIEW ARTICLE

Nosocomial Pneumonia: An Update on Early Diagnosis and Prevention

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Abstract: Nosocomial pneumonia and nosocomial tracheobronchitis present a significant problem of anesthesiology and critical care medicine. This review presents the results of our own research on the usefulness of new molecular biomarkers in the early diagnosis of nosocomial pneumonia, as well as modern principles for its prevention. A promising direction for the early diagnosis of nosocomial pneumonia and its complications is the study of new molecular biomarkers, in particular, Club cell protein and surfactant proteins. Effective prevention of nosocomial pneumonia should be based on a complex of modern evidence-based methods.

Keywords: Biomarkes, diagnosis, nosocomial pneumonia, prophylaxis, sepsis, fever.

1. INTRODUCTION

The aim of this review is to analyze the recent data on the new approaches for early diagnosis of nosocomial pneumonia and modern principles for its prevention.

The search for publications was carried out in the Scopus and PubMed databases; search for Russian language publications was carried out in elibrary.ru database. A search was made for publications (literature reviews, observational studies, double-blind randomized studies) for the period 2000-2019. The following search queries were used: “inhaled antibiotics prevention”, “nosocomial pneumonia prevention”, “nosocomial tracheobronchitis prevention”, “nosocomial pneumonia biomarker”, “Club cell protein”. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as reference: number of records identified through database searching was 2969, number of records after duplicates removed was 1535, number of records screened was 1434, number of records excluded was 914, number of full-text articles assessed for eligibility was 520, number of studies included in qualitative synthesis was 81.

2. THE PROBLEM OF NOSOCOMIAL PNEUMONIA IN CRITICAL CARE MEDICINE

Nosocomial Pneumonia (NP) is a disease characterized by the appearance of the new focal-infiltrative changes on the chest X-ray 48 hours or more after hospitalization combined with the clinical data confirming their infectious nature (a new wave of fever, purulent sputum or purulent discharge of tracheobronchial tree, leukocytosis, etc.) with the exclusion of infections that existed in the incubation period at the time of hospital admission [1].

Nosomial Tracheobronchitis (NT) associated with mechanical ventilation is a tracheobronchitis that developed no earlier than 48 hours after the intubation of the trachea and the start of the mechanical ventilation, in the absence of signs of pulmonary infection at the time of intubation [1].

Nosocomial tracheobronchitis (NT) is an intermediate stage between the colonization of the lower respiratory tract and the nosocomial pneumonia, which develops in 10-30% of critically ill patients on mechanical ventilation, the mortality in this category of patients is up to 76% (attributable mortality about 10%). The concept of NT is of fundamental importance in critical care medicine: nosocomial tracheobronchitis and nosocomial pneumonia make up a continuum. Focusing our preventive and treatment measures on NT (as intermediate stage between airway colonization and pneumonia) may be promising in preventing the development of NP in critically ill mechanically ventilated patients [1, 2, 7, 8].

According to Yakovlev S. et al. [9] the prevalence of nosocomial infections in hospitals in Moscow is 7.61%, community-acquired infections - 28.53%. The highest prevalence of nosocomial infections was observed in the intensive care units - 26.28% and neurology units - 13.73%. The prevalence of nosocomial infections in medical and surgical departments was about the same - 4.76% and 4.12%, and in urology departments - the lowest (2.92%). Among nosocomial infections, lower respiratory tract infections were the most prevalent (42.4%). Pathogens of nosocomial infections in adults were characterized by multiple antibiotic...
resistance. Nosocomial pneumonia is the most common nosocomial infection in mechanically ventilated patients (9-27%). In Russia in 2006 25,852 cases of NP (incidence of 0.8 / 1000 patients) were reported. Nosocomial pneumonia develops in 0.5-0.8% of hospitalized patients, and is 10-15 times more prevalent in intensive care units [1-9].

The classical diagnostic features of nosocomial tracheobronchitis include: temperature above 38°C, leukocytosis greater than 12*10⁹/L or leukopenia below 4*10⁹/L, plus purulent sputum with an increase in its quantity, an increased need for the upper airways suctioning, and also presence of wet wheezes in the lungs. An important diagnostic sign of NT (in contrast to nosocomial pneumonia) is the absence of new infiltrates on the chest X-ray [1, 5].

Another approach to the diagnosis of NT is based on a systematic daily study of the secretion of the lower respiratory tract in order to determine the moment of colonization, the spectrum of microorganisms, their sensitivity to antibiotics, which allows the initiation of early targeted antibiotic therapy and thereby prevent the development of NP (in 60-88% of cases, NT is caused by gram-negative microorganisms [1, 5]).

In the United States, the concept of ventilator-associated event - VAE (event associated with mechanical ventilation), which combines ventilator-associated condition - VAC (condition associated with mechanical ventilation), infection-related ventilator-associated complication - IVAC (infection-related complication developed during mechanical ventilation) and possible VAP (possible pneumonia on the background of mechanical ventilation). Diagnostic criteria for VAE are the following: deterioration of oxygenation after a period of stability or improvement of the patient’s clinical status; signs of systemic infection; laboratory signs of respiratory tract infection. Radiographic signs, as the most subjective, are excluded from the VAE diagnostic algorithm. This “event” can be caused by a variety of reasons, such as NP, nosocomial tracheobronchitis, acute respiratory distress syndrome, cardiogenic and non-cardiogenic pulmonary edema, pulmonary thromboembolism, atelectasis, etc. The use of epidemiological criteria allows to identify groups of patients with the greatest risk of intestinal infections, compare the situation in various institutions, evaluate the effectiveness of epidemiological measures, identify problems and plan algorithms for solving them [10]. In Europe these criteria are not used.

3. EMERGING APPROACHES TO NOSOCOMIAL PNEUMONIA DIAGNOSIS - CLUB CELL PROTEIN AND SURFACTANT PROTEINS

Early diagnosis of NP and its complications is based on the use of sensitive and specific molecular biomarkers in combination with clinical and instrumental methods.

The experience of using complex clinical, laboratory and instrumental methods of NP diagnosis shows that NP diagnosis is reliable in the presence of clinical, radiological and microbiological criteria. Criteria for the diagnosis of NP are well known and set out in various national resources, e.g., in the Russian National Guidelines [1]. The full range of criteria is performed only in 31% of patients. In 47% of patients, only a combination of clinical and laboratory or clinical and radiographic, or laboratory and radiological criteria is detected. In 22% of patients, only one of the three groups of diagnostic signs can be identified, which makes NP diagnosis doubtful [5, 6]. Biomarkers are of great perspective for the diagnosis and monitoring of the effectiveness of NP treatment, since they make it possible to obtain information on the patient's condition in the shortest possible time and least invasively. Any biomarker should be used only in combination with the clinical assessment of the patient [6, 11].

Club cells are non-mucus producing cells located in the terminal bronchioles. In human lungs they make up 15-20% of epithelial cells, while in the lungs of mice they make up 70-90%. Club cells secrete a number of biologically active substances that are involved in the protection and repair of bronchiolar epithelium, mucus degradation, regulation of inflammation, detoxification of xenobiotics (Club cell protein (CCP), surfactant proteins A, B, D, Club cell tryptase, pro-inflammatory cytokines, etc.) [12, 13].

These secretory cells in the terminal bronchioles were first described by the German anatomist Max Clara (1899-1966) in 1937 [14, 15]. Since 1955, the term “Clara cells” (CC10, CC16, uteroglobin) [16] has appeared in the literature, the Clara cell protein was discovered in 1984 [17]. The number of publications on this topic is continuously increasing [15, 16]. Considering that the biological material in which Max Clara studied these cells was obtained from executed prisoners of concentration camps in Germany [18, 19], it is currently not recommended in the English-language literature to use the eponym “Clara cell protein”, but to replace it with “Club cell protein”.

The Club Cell Protein is a 16 kDa protein. CCP is also expressed in small amounts in the prostate, thyroid, breast, and epiphysis. In the lungs CCP is the most common among the other extracellular fluid proteins. The function of the Club cell protein is not completely clear, but it is obvious that it plays an important role in anti-oxidant and anti-inflammatory defense of the lungs. Its release inhibits phospholipase A2 and chemotaxis of macrophages and neutrophils, modulates the activity of interferon-gamma and tumor necrosis factor alpha (TNF-α). In vivo studies showed that in CCP-deficient mice the severity of the inflammatory response to bacterial and viral infections was greater, but the killing of bacteria in the lungs did not change. A number of studies proved that CCP limits the severity of the inflammatory response in the lungs [11-19].

The Club cell protein was investigated in many studies as a marker of damage to the lung epithelial barrier and the activity of the local immune system of the lungs in idiopathic pulmonary fibrosis, sarcoidosis, chronic obstructive pulmonary disease, asthma, bronchiolitis obliterans, etc. Club Cell Protein content in the blood plasma is reduced in chronic lung diseases due to Club cells destruction, but it is significantly increased in acute lung diseases. Considering the biological function of Club cells and CCP, an increase in CCP content in the blood plasma of patients in critical
According to a study by Vanspauwen M. et al. in [18-20], the Club cell protein (CCP) is widely discussed as a molecular biomarker for both acute respiratory distress syndrome (ARDS) and nosocomial pneumonia (NP) [17-21]. Our studies proved that Club Cell Protein (CCP) is a sensitive and specific diagnostic molecular biomarker for the presence of Pseudomonas aeruginosa in NP: Club cell protein content in this case is ≤ 17.5 ng/ml, the diagnostic range is 4.5-15.2 ng/ml, sensitivity 92.7%, specificity 72.0%, area under the curve 0.84; 95% confidence interval 0.713-0.926; p< 0.0001. In addition, according to the results of our study, we developed a laboratory method for evaluating the effectiveness of inhaled antibiotic therapy in patients with NP, including monitoring the CCP content in blood before the start of antibiotic therapy and after the first inhalation of antibiotic. The idea of this method is characterized in that the CCP content in venous blood serum is determined 1 hour before the first antibiotic inhalation and 1 hour after inhalation using enzyme immunoassay; an increase in the CCP content at least 1.5 times indicates the effectiveness of inhaled antibiotic therapy [22].

An increase in blood CCP in ARDS is associated with damage to the structures of the air-blood barrier and terminal bronchioles, followed by protein penetration into the blood. According to Dettermann R. et al. (2009) the development of ARDS in NP is accompanied by a threefold increase in plasma CCP [23]. The content of CCP in bronchoalveolar fluid (BAL) can act as a predictor of the development of ARDS in critically ill patients [24]. According to a prospective multicenter study of Lesur P. et al. (2006) CCP content was higher in those who died than in survivors [25]. A significant contribution to an increase in the level of CCP in the BAL in patients with ARDS plays mechanical ventilation [19]. In a study by Lin J. et al. (2018) it was proved that CCP was a sensitive (90.4%) and specific (79.8%) marker of the damage to the structures of the air-blood barrier in ARDS patients (diagnostic level 33.3 ng/ml) [26], it correlates with the degree of severity ARDS (i.e. with the degree of damage to the structures of the air-blood barrier), the CCP level was higher in the deceased patients and was associated with a longer intensive care unit stay.

There are separate studies on small heterogeneous samples of patients with conflicting results on the informativity of CCP in the diagnosis of NP [18-20]. According to a study by Vanspauwen M. et al. (2011) CCP content in BAL was higher in patients with NP compared with patients without NP, but in this study, unlike ours, the content of CCP in BAL was studied [12]. In the study of Negrin L et al. (2017) it was shown that the Club cell protein (30.51 ng/ml on the second day after polytrauma, sensitivity 71.4%, specificity 69.85%) was informative for predicting the development of NP on the background of ARDS in polytrauma patients [27].

The data we obtained on the informativity of CCP for the diagnosis of the presence of Pseudomonas aeruginosa in the BAL with NP in abdominal surgical patients are of considerable scientific novelty and have practical significance. No similar clinical studies were found in a similar category of patients in the available databases. About 20% of NP is caused by Pseudomonas aeruginosa. In the Russian Federation, this pathogen colonizes sputum in 12.1% of cases according to the data for 2013-2014. The outcomes of NP treatment in this group of patients are the worst: the overall mortality rate reaches 70%, attributable mortality - 40% [28]. The described decrease in CCP content in the blood plasma of NP patients induced by Pseudomonas aeruginosa represents the new data on the pathogenesis of NP in patients with abdominal surgical infection and is probably not due to the destruction of Club cells, but due to a decrease in CCP synthesis in Club cells. The results of our study are supported by data from a number of experimental studies in which Pseudomonas aeruginosa was shown to strongly inhibit the expression of the proximal part of the promoter of the CCP gene in alveologes. The inhibition of the promoter activity of this gene is mainly caused by TNF-α secreted by Pseudomonas aeruginosa. It is known that infection of the lungs caused by Pseudomonas aeruginosa is accompanied by a significant increase in the plasma and sputum TNF-α, which in turn inhibits the synthesis of CCP in Club cells. In the study of Hayashida S. et al. on the CCP gene knockout mice it was shown that intratracheal administration of the Pseudomonas aeruginosa culture inhibits the protein synthesis of Club cells (decreases within 1-5 days of infection, the synthesis is restored by the 14th day after infection; it should be noted that experimentally it was proven to decrease CCP synthesis without damaging Club cells), which is associated with a more pronounced inflammatory response in the lungs. In the research work of Harrod K. et al. neutralizing antibodies against human TNF-α have been shown to cause reversal of this effect on the promoter of the CCP gene. A reverse explanation is also possible - in mice deficient in CCP expression the cellular response to inhalation of Pseudomonas aeruginosa lipopolysaccharide is much more pronounced. Our study for the first time confirmed the results of these experimental studies in the clinic [29, 30].

Surfactant proteins are an important part of the human pulmonary immune system. The human lung surfactant is a multi-molecular complex consisting of phospholipids and cholesterol (only 90%) and surfactant proteins (10%). Surfactant proteins are composed of high molecular weight hydrophilic proteins, Surfactant Proteins-A (SP-A) and SP-D, and low molecular weight SP-B and SP-C, which are
necessary for the formation of the biophysical properties of the surfactant. Surfactant is not only a surface-active substance in the lungs, but also participates in mucociliary clearance and fluid exchange in the lungs [31]. Surfactant Protein D (SP-D) is a pattern recognition molecule that belongs to the family of collectins. Human collectins also include surfactant protein A (SP-A), which has an organism distribution and functions that overlap with SP-D. The main function of SP-D is regulation of the level of surfactant lipids, as well as participation in the phospholipid homeostasis outside the lungs. In addition, SP-D is expressed in muscle cells and the endothelium, where it functions as an anti-inflammatory substance [21].

In our study we established that surfactant protein D was a sensitive and specific diagnostic molecular biomarker of the damage to the structures of the air-blood barrier in NP patients with ARDS as a complication: surfactant protein D content was ≥111.2 ng/ml, sensitivity 68.2%, specificity 92.3%, the area under the curve is 0.85; 95% confidence interval 0.684-0.945; p <0.0001. A combined analysis of the content of surfactant protein D in blood, oxygenation index and extravascular lung water index significantly increased the area under the curve: sensitivity 81.0%, specificity 100.0%, diagnostic level of surfactant protein D > 93.7 ng/ml (area under curve 0.96; 95% confidence interval 0.817-0.998; p <0.0001), oxygenation index <280, extravascular lung water index > 8.3 ml/kg [32].

In ARDS an increase in plasma SP-D is due to the damage to the structures of the air-blood barrier with an increase in its permeability to SP-D, as well as the proliferation of type II alveolocytes and an increase in SP-D synthesis. The content of SP-D in the blood plasma reflects the degree of damage to the cells of the alveolar epithelium type II and the increase in the permeability of the air-blood barrier in ARDS. Very little research exists on the diagnostic value of SP-D in NP. No studies were found on the SP-D dynamics in the case of NPs complicated by ARDS, as well as on the joint analysis of SP-D, oxygenation index and extravascular lung water index. In mice deficient in SP-D the cellular reaction in the lungs is much more pronounced in response to LPS instillation [18]. In children with NP the content of SP-D in BAL increases, and this increase is most pronounced in patients with Pseudomonas aeruginosa in BAL [33]. These data are confirmed in a study of Tekerek N. et al. [34]. In the work of Park J et al. [35] it was proved that SP-D blood levels were higher with ARDS developing on the background of NP (87% of patients in this study had direct ARDS), with SP-D sensitivity for diagnosing ARDS being 74%, specificity 63%, area under ROC curve 0.71 (SP-D content 12.7 ng/ml). It is known that the blood level of SP-D is higher with direct ARDS than with indirect.

Thus, new molecular biomarkers present a significant perspective for the development of modern approaches of early diagnosis of nosocomial pneumonia.

4. PREVENTION OF NOSOCOMIAL PNEUMONIA

The principles of NP prevention are based on our knowledge of the risk factors, etiology and pathogenesis of this infectious complication of critical conditions [1, 2]. The risk factors for NP associated with the course of the underlying disease include: advanced age, male gender; alcoholism and drug addiction; the presence of severe concomitant diseases (chronic obstructive pulmonary disease, diseases of the central nervous system, peptic ulcer); the level of consciousness of the patient; the severity of multiple organ failure, especially renal failure; ARDS, extracorporeal oxygenation; condition after cardiac arrest and cardiopulmonary resuscitation; burns; postponed emergency surgery; reoperation; previous surgery (neurosurgery, thoracic surgery, cardiac surgery); malnutrition; immunosuppression of various genesis; prolonged bed rest, tube feeding, dysphagia, aspiration, pronounced pain syndrome [36-40]. The risk factors for NP associated with the invasive nature of the treatment process include: perioperative blood transfusion; tracheal intubation or tracheostomy lasting more than 48 hours, reintubation, emergency intubation; frequent changes in the respiratory circuit; horizontal position of the bed head; use of a nasogastric tube; the need for invasive monitoring, long-term use of invasive devices; transporting the patient [36-40].

Nosocomial pneumonia can also develop due to the presence of deficiencies in the organization of the treatment process: overcrowded departments, lack of staff and space, lack of consumables, lack or insufficiency of special staff training, non-compliance with the rules of prevention and the lack of a system for monitoring nosocomial infections with analysis of resistance of strains to antibiotics and disinfectants [41, 42].

The general measures for the prevention of any nosocomial infection include: epidemiological surveillance and local microbiological monitoring; isolation of patients with infectious complications and carriers of multidrug-resistant bugs; sufficient staffing of the department, personnel training in evidence-based methods of patient care; use of disposable consumables; compliance with the recommendations on the strategy and tactics of antimicrobial therapy; reduction of the perioperative period; early rehabilitation in the postoperative period; timely rehabilitation of extrapulmonary foci of infection; timely removal of all invasive devices; hand processing by staff [40-42].

Prevention of NP should include a set of measures, including the most effective ones and eliminating potentially harmful procedures. Separate measures will not be effective [43-46].

4.1. Treatment of the Oral Cavity with an Aqueous Solution of Chlohexidine [47]

Treatment of the oral cavity with antiseptics was chosen as a prophylaxis for NP based on the concepts of the pathogenesis of NP - microaspiration of the oral contents. The first study of chlohexidine was conducted in 1996 - a 69% decrease in the NP incidence was demonstrated; mortality in the chlorhexidine group was 1.2% versus 5.6% in the group without it [48]. This antiseptic was chosen primarily with a view to its safety in dentistry [49, 50]. A
large meta-analysis of 2007 [51] showed a 40% decrease in the NP incidence; in a subsequent meta-analysis of 2011 [52] 33% decrease of NP incidence was shown, and in the 2016 Cochrane Review a 26% decrease of NP incidence was shown [53]. Treatment of the oral cavity with a solution of chlorhexidine was included in the international and national guidelines [54, 55]. However, the effectiveness of this technique was never proven in any randomized study, and meta-analyses were performed on different groups of patients with different duration of mechanical ventilation, as well as blind and open research. In addition the diagnostic criteria for NP are subjective and low-specific [56].

In a meta-analysis [57] in which patients of cardiac and non-cardiac surgery were analyzed separately, it was shown that the reduction in the incidence of NP development was primarily due to the results of studies in the category of cardiac surgery patients. There was no effect on the duration of mechanical ventilation, duration of intensive care unit or hospital stay. Moreover, it was shown that mortality was higher in the chlorhexidine group, which is especially pronounced in the category of non-cardiac surgery patients. The mortality correlates well with the increase in the concentration of chlorhexidine solution, which is used to treat the oral cavity [58, 59].

Increased mortality related to the use of chlorhexidine may be possibly associated with the microaspiration of part of the antiseptic and with the subsequent development of ARDS [60-63] or with the systemic toxicity of the drug [64]. Another possible risk associated with oral chlorhexidine treatment is the damage to the oral mucosa when using a 2% solution [65].

According to the latest meta-analysis [47], the effectiveness of this technique has been proven exclusively in the category of cardiac surgery patients who are on a ventilator for no more than 24 hours. It is also necessary to take into account the methodological aspects of studies on the effectiveness of chlorhexidine in the prevention of NP: treatment of the oral cavity with chlorhexidine (antiseptic) inevitably reduces the frequency of positive cultures of sputum [48]. In the single-center retrospective study Deschepper M [66] (2018), an increased risk of death was observed with the use of chlorhexidine.

4.2. Raising the Head end of the Bed by 35-40° [67, 68]

Reduces the incidence of NP but there is no effect on the duration of mechanical ventilation, duration of the intensive care unit stay and mortality. In the Spanish study an attempt was made to use the lateral patient position with the head end of the bed lowered (lateral Trendelenburg) for the prevention of NP [69]: the incidence of NP in this group was lower, but no effect on other outcomes was found (duration of mechanical ventilation, duration of the intensive care unit stay and mortality). In the lateral Trendelenburg position group vomiting was more prevalent. Positioning the patient is a simple approach which can be implemented in any intensive care unit.

• Change the breathing circuit only when there is visible contamination or breakage.
• Protocolized prevention of deep vein thrombosis.
• Minimization of sedation, daily sedation interruptions [70-73].
• The use of endotracheal tubes with subglottic aspiration - according to the latest meta-analysis the effect of this technique on the duration of mechanical ventilation, duration of intensive care unit stay and mortality was proven [74]. Currently, there is no evidence that the specialized design of the cuff of an endotracheal tube in any way reduces the frequency of NP development or affects the outcomes [75].
• Probiotics - can reduce the frequency of NP, but do not affect other outcomes. The results of these studies are largely dependent on the microbial composition of the drugs used [76-78].

4.3. Selective Decontamination of the Oral Cavity or the Gastrointestinal Tract

This preventive measure works effectively in countries with low antibiotic resistance, for example, the Netherlands, where the main positive results on this problem were obtained. It should be noted that the prevention of stress ulcers of the gastrointestinal tract is associated with an increased risk of developing NP [79, 80].

• The preferred use of non-invasive ventilation is if the clinical situation allows [1, 2].
• The protocolized weaning approach [1, 2].
• One of the alternative approaches that require further investigation is the use of inhaled antibiotics for nosocomial tracheobronchitis to prevent the development of NP. The data from a large meta-analysis of 2016 showed that at present, there is insufficient evidence to recommend the use of inhaled antibiotics in NT [81]. On the other hand, according to the most up-to-date meta-analysis in 2018, the use of inhaled antibiotics in NT can reduce the frequency of NP development (OR 0.53; 95% CI 0.34-0.84), but does not affect mortality. Moreover, this effect is most pronounced in inhalation of antibiotics (OR 0.46; 95% CI 0.22-0.97), but not in intratracheal instillation of antibiotics (OR 0.57; 95% CI 0.28-1.15) [82].
• An alternative prophylactic approach is the use of intravenous antibiotics for NP prophylaxis. Badve M et al. (2018) proved that preventive antibiotics reduced the risk of post-stroke pneumonia [83]. Klompas M. et al. (2017) showed that very short antibiotic courses (1-3 days) were associated with outcomes similar to longer courses (>3 days) in patients with NP [84]. The latest trial proved that administration of prophylactic piperacillin-tazobactam reduced only early-onset NP, but the
benefit does not extend to late-onset NP [85]. But all the possible risks of any antibiotic prophylaxis should be taken into account and it must be tailored to the needs of a high-risk patient and the identified pathogen [86].

- Probably the most easy to implement, but least evidence-based is physical therapy. Lopez-Lopez L et al. (2019) showed that an integrated programme of physical and electrical therapy for NP patients improves physical and functional performance in patients [87].

CONCLUSION

Thus, nosocomial pneumonia and nosocomial tracheobronchitis present an urgent problem of critical care medicine. A promising direction for the early diagnosis of nosocomial pneumonia and its complications is the study of new molecular biomarkers, in particular, Clara cell protein and surfactant proteins. Effective prevention of nosocomial pneumonia should be based on a complex of modern evidence-based methods.

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CONFLICT OF INTEREST

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REFERENCES


