POST-OPERATIVE RISK OF BISPHOSPHONATE-RELATED OSTEONECROSIS COMPLICATION. IS ANTIMICROBIAL PROPHYLAXIS REQUIRED IN PATIENTS CLASSIFIED AS LOW- AND MEDIUM-RISK GROUPS OF BISPHOSPHONATE-RELATED OSTEONECROSIS COMPLICATION?

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Dear Editor,

With a great interest, we have familiarized ourselves with the latest recently published recommendations of the Polish Dental Association entitled "Rekomendacje Grupy Roboczej Polskiego Towarzystwa Stomatologicznego i Narodowego Programu Ochrony Antybiotyków" (Polish Dental Association and National Programme to Protect Antibiotics Working Group recommendations for administration of antibiotics in dentistry). The first such publication in Poland, of utmost importance for patients, dental practitioners, and scientists, provides the current evidence-based criteria of applying antibiotic therapy as a part of antimicrobial protocol for invasive dental procedures within maxilla-facial region.

We would like to express our gratitude for the work of the team of experts who gathered the data and prepared the final version of recommendations, which are so crucial from clinical and medico-legal points of view. In relation to the rapidly increasing burden of resistance to drugs, it seems of key importance to reduce the scope of indications for systemic antibiotic therapy in the treatment area of endodontics, periodontology, and oral surgery.

Most of developed countries have similar suggestions, guidelines, and/or recommendations, being an element of public health activities and good practice in medicine, which have been established with participation of scientific associations, independent experts, and scientists. We paid particular attention to a recommendation 1.10, which concerns patients treated with antiangiogenic medications from bisphosphonates group as well as risk of bisphosphonate-related osteonecrosis of the jaws (BRONJ) incidents following dental surgical procedures.

"1.10. Specific recommendation for antibiotic prophylaxis against surgical site infections in patients on antiresorptive/antiangiogenic therapy".

"It is recommended to administer antibiotic prophylaxis in patients taking bisphosphonates, denosumab, or bevacizumab before any surgical procedure involving bone surgery (e.g. exodontia, dento-alveolar surgery, endodontic, or periodontal surgery); antibiotic therapy should be initiated one day before the surgery and continued until the 3rd post-operative day (short-term prophylaxis), with the exception of cases with concurrent risk factors for medication-related osteonecrosis of the jaw (therapy with zoledronic acid, intravenous route of bisphosphonate administration, therapy > 3 years, previous episode of osteonecrosis of the jaw), where antibiotic prophylaxis should be continued until 14th day after the surgery (long-term prophylaxis)".

Taking into account the prevalence of pharmacological treatment with bisphosphonates, its importance from public health perspective, and an increasing bacterial resistance to standard antibiotic therapies, it is well justified to undertake wise and careful decisions concerning prophylaxis with the use of antibiotics, par-

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ticularly in case of low-risk post-operative BRONJ complications.

From the analysis of available data, using databases of PubMed Central, Medline, Scopus, Embase, meta-analyses, and available guidelines from Europe, USA, and Australia, one can see that most of the guidelines or recommendations classify patients into 2 or 3 risk groups regarding the risk of post-operative BRONJ, namely low-, medium-, and high-risk. For category one (low-risk), the current guidelines unequivocally recommend not to use a routine antibiotic cover. It is very significant to note that systemic prophylaxis of post-operative infections by means of systemic antibiotics is controversial also in patients from the high-risk group of BRONJ occurrence. The Scottish Dental Clinical Effectiveness Programme (SDCEP, Scotland, UK) provides detailed recommendations for A/M groups of patients. Moreover, there are recommendations, which have been in use since 2010 in Australia: "For the greater majority of patients, who are taking oral bisphosphonates requiring routine dental treatment, including extractions under local anesthetic in the dental chair, do not require any special precautions. (Section 4.1.3)".

Examples of existing guidelines (quoted directly in English):

1. "Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone impacting treatments specifically to reduce the risk of MRONJ (strong recommendation; low quality evidence). There is currently insufficient evidence to support the use of antibiotic or topical antiseptic prophylaxis to reduce the risk of MRONJ following extractions or procedures that impact on bone".

2. "There is no evidence that pre- and post-operative antibiotics are effective in preventing BRONJ, although some experts have recommended their use based on a hierarchy of risk".

3. "The use of an antibiotic regimen to lessen the risk of BRONJ from occurring in patients at high-risk for BRONJ is controversial, and expert opinion is divided on the appropriateness of this approach".

4. "No special precautions indicated. Use of recommended protocol, using protracted antibiotic prophylaxis pre- and post-treatment NOT indicated. Proceed with all routine non-invasive dental care, and any routine dental extractions or oral surgery (if so indicated)".

5. "There is minimal evidence to say the use of prophylactic antibiotics will reduce MRONJ".

6. "Antibiotic cover is not proven but carried out by many treating these cases".

Literature presented in the Work Group Recommendations regarding the risk of BRONJ and the use of antibiotics (items 9 and 51, level C of scientific reliability), is devoted mainly to the use of bisphosphonates applied intravenously in case of neoplasms treatments. In connection with this, the above category of patients belongs to high-risk group of developing BRONJ after the surgery. It does not comprise the low-risk group of patients, since the majority of patients are taking the medication orally, due to osteoporosis among others. As mentioned in the Recommendations, the guidelines are based on experts' opinions or results of retrospective studies (level C of data) or are provided based on data derived from randomized clinical trials (level B). Unfortunately, outcomes of RCT studies with the highest reliability level A are not available.

Considering the above, we propose to develop a separate set of recommendations for low- and high-risk groups of BRONJ, depending on the type of therapy and primary medical condition. We believe that our remarks will be treated as an invitation for further discussion and continuation of work aimed at optimizing the recommendations concerning prophylaxis and treatment by using antibiotics in dentistry.

Current valid international recommendations regarding systemic cover with antibiotics in case of enhanced risk of BRONJ:

1. Dental Management of Patients Prescribed Bisphosphonates – clinical guidance produced in conjunction with the Dental LPN for Shropshire and Staffordshire Department of Oral and Maxillofacial Surgery, University Hospitals of North Midlands NHS Trust, UK.

2. Oral Health Management of Patients Prescribed Bisphosphonates – this guidance aims to minimize the risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ) developed in patients who are on bisphosphonate medications. It is based on guidance provided by the Scottish Dental Clinical Effectiveness Programme (April 2011) and Mr. Simon Hodder (consultant in oral and maxillofacial surgery, ABMU Health Board).

3. Oral Health Management of Patients Prescribed Bisphosphonates – Bisphosphonates Cover published in April 2011; withdrawn April 2017. Superseded by Oral Health Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw published in March 2017.

4. Prevention of Osteonecrosis of the Jaw (ONJ) in Patients on Bisphosphonate Therapies – document number GL2010_010; published on 23rd July 2010 by Centre for Oral Health Strategy.

5. Dental extractions and bisphosphonates: the assessment, consent, and management, a proposed algorithm. Malden N et al. British Dental Journal 2009, Vol. 206, No. 2.

6. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw, 2009 update.

7. Oral Health Management of Patients Prescribed Bisphosphonates – Summary Guidance. Scottish Dental Clinical Effectiveness Programme, April 2011.

8. Bisphosphonates Fact File. British Dental Association, September 2008.