Prevention of infection after knee arthroplasty
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Health political and scientific background
Man-made joints for implantation in the human body, so called joint endoprostheses, including knee endoprostheses, are frequently used in persons with irreversible diseases of the joints for the reduction of movement restrictions and pain as well as for the improvement of their quality of life. The number of primary implantations of knee total endoprostheses and the number of revisions of knee endoprostheses (including revisions of single parts) are high, 146,052 and 10,387 interventions respectively in 2008. Due to the demographic change it can be expected that the importance of knee replacements will increase in the future.

The implantation of a joint endoprosthesis (arthroplasty) is associated with the general risks of a major surgery and with the specific risks linked to this procedure, mainly the risk of an infection around the implanted endoprosthesis. An infection after the joint replacement operation is a relatively rare, however a very severe complication, that can lead to revision operations, a restriction of the patient's mobility and even death. Due to the increasing number of joint replacement operations, these infections will become more important and lead to high costs.

Different interventions are used for the prevention (or prophylaxis) of infections. These interventions can be performed pre-, peri- as well as postoperatively and can be subdivided in interventions without and with the use of antibiotics (hygiene interventions and antibiotic prophylaxis). Most hygiene interventions as well as perioperative systematic antibiotic prophylaxis are not specific for the joint arthroplasty. The possibility of using antibiotics in bone cement is a special feature of joint arthroplasty. Systematic reviews on the importance of the hygiene interventions as well as on antibiotic prophylaxis in the knee arthroplasty are still missing. The medical effectiveness, cost-effectiveness as well as ethical, social and legal implications of these interventions are therefore not clear and will be systematically evaluated in the presented report.

Research questions
Medical evaluation
The medical evaluation deals with the following question:
What is the effectiveness of the interventions to prevent infections after knee arthroplasty?

Health economic evaluation
The health economic evaluation aims to answer the following question:
What is the cost-effectiveness of the interventions to prevent infections after the knee arthroplasty?

Ethical, social and legal aspects
The ethical, social and legal evaluation deals with the following question:
Which ethical, social and legal implications can be expected in the use of interventions to prevent infections after knee arthroplasty?

**Methods**

**Medical evaluation**

A systematic literature search is conducted in the medical electronic databases MEDLINE, EMBASE, SciSearch etc. in June 2009 and is restricted to the languages German or English. The evaluation includes only published data. The selection of the relevant publications has been performed by two independent reviewers, both experienced in evidence-based medicine procedures.

The analysis includes publications which describe and/or evaluate clinical data from randomized controlled trials (RCT), systematic reviews of RCT, registers of endoprostheses or databases concerning interventions to prevent infections after knee arthroplasty. Only interventions with the explicit objective to decrease the rate of infections after knee arthroplasty (i. e. no blood transfusion etc.) are defined as interventions to prevent infections.

Additionally, a hand search in the reference lists of the relevant articles as well as on the web pages of joint endoprostheses registers (e. g. annual reports) has been conducted with respect to further information concerning interventions to prevent infections after knee arthroplasty.

As the interventions to prevent infections after knee arthroplasty are very diverse and mostly unspecific, the evaluation of hygiene interventions is based on the recommendations of the commission for hospital hygiene and infection prevention at the Robert Koch Institute (RKI) “Prevention of postoperative infections in the operation area”. Subsequently, an analysis of the identified systematic reviews on hygiene interventions in knee arthroplasty is performed.

The evaluation of the importance of antibiotic prophylaxis in the knee arthroplasty is based on the systematic reviews as well as on the newly published and, therefore, not included RCT in these systematic reviews. This analysis includes data on the comparison of antibiotic prophylaxis (intravenous and/or in cement) versus no antibiotic prophylaxis, intravenous antibiotic prophylaxis versus antibiotic prophylaxis in cement, combined antibiotic prophylaxis (intravenous and in cement) versus non-combined antibiotic prophylaxis (intravenous or in cement) and on the comparison of different antibiotic drugs. However, it does not evaluate studies on the comparison of different drug dosages and dose distributions.

The synthesis of information from different publications has been performed qualitatively.

**Health economic evaluation**

To be included in the analyses, publications found by the performed literature search (s. above) should describe and/or analyse health economic evaluations from RCT, systematic reviews of RCT, registers of endoprosthesis or databases concerning interventions to prevent infections after knee arthroplasty.

**Ethical, social and legal aspects**

The conducted literature search (s. above) aims also to identify publications dealing explicitly with ethical, social or legal aspects in the use of interventions to prevent infections after knee arthroplasty.
Results

Medical evaluation

Results of the literature search
The systematic literature search yields 1,030 hits. Based on the predefined inclusion and exclusion criteria, the analysis includes ten publications identified through the literature search and one through the hand search. The recommendations of the commission for hospital hygiene and infection prevention of the RKI “Prevention of postoperative infections in the operation area” have been used as a basis for the evaluation of hygiene interventions. Only one systematic review is included from further publications on hygiene interventions in knee arthroplasty.

Four systematic reviews are identified concerning antibiotic prophylaxis in knee arthroplasty. One of these systematic reviews is the publication with the most current literature search as well as with the highest number of considered studies. This review is selected as a basis for the evaluation of the antibiotic prophylaxis in knee arthroplasty. Since only two of the RCT considered in this publication have been conducted exclusively on patients after knee arthroplasty, both using cefuroxim-impregnated cement, these RCT have been primarily analysed in the presented report. Additionally, the presented analysis includes two newly published RCT, which are not considered in the identified systematic reviews. Both RCT evaluate antibiotic prophylaxis in knee arthroplasty, one to vancomycin-impregnated cement and another to mupirocin nasal ointment.

Three articles concerning interventions to prevent infections after knee arthroplasty are selected from publications on data analyses from endoprostheses registers or databases.

Hygiene interventions
Numerous hygiene interventions are recommended as interventions to prevent postoperative infections in the operation area. The recommendations are not indication-specific. They are usually summarized on the basis of results from studies on different indications, from non-randomized studies and/or from data on clinically irrelevant endpoints (for example bacterial contamination).

The included systematic review analyses on the basis of RCT the effectiveness of closed suction drainages (systems to drain wound secretions) in orthopedic surgery (in general) with respect to the risk for wound infections. It provides no evidence for the effectiveness of closed suction drainages. In addition, none of the evaluations from the endoprostheses registers and databases reveals strong hints for the effectiveness of any hygiene intervention in knee arthroplasty.

Antibiotic prophylaxis
RCT on the comparison of intravenous antibiotics versus no antibiotic prophylaxis in knee arthroplasty are not found. The identified registers and databases also do not compare these therapy options. On the basis of randomized studies evidence exists only for the effectiveness of intravenous prophylaxis with antibiotics in hip arthroplasty. In the recommendations this evidence is externally transferred to arthroplasty of all joints including knee replacement.

Randomized studies on the comparison of antibiotic prophylaxis exclusively in cement versus no antibiotic prophylaxis in knee arthroplasty are not identi-
The included endoprostheses registers and databases also do not compare these treatment options. No significant difference in the effectiveness of the investigated intravenous antibiotics is demonstrated.

Three RCT are published on the additional effect of antibiotics in cement by intravenous antibiotic prophylaxis. All three show a statistically significant reduction in the rate of deep infections while using the antibiotic additionally in cement. However, these studies have some flaws with respect to their methodological quality. Moreover, all these studies have been performed in the same clinical center as well as in operating rooms without clean-air measures (laminar flow, space suits etc.). Considering the data for protocol violations the risk of bias in the conducted metaanalysis is substantially decreased. The estimated relative risk is 0.21 (95% confidence interval from 0.06 to 0.74). A significantly lower rate of revisions due to infections for the combination of antibiotic prophylaxis, intravenous and in cement, in comparison to the exclusive intravenous prophylaxis is also shown in the Finnish endoprostheses register.

The single RCT on the effectiveness of mupirocin nasal ointment in the prevention of postoperative wound infections finds overall low event rates in both groups with and without use of the mupirocin ointment as well as no significant differences between the groups.

**Health economic evaluation**
The systematic literature search on health-economic evaluation yields 177 hits. Although one publication presents a cost-effectiveness analysis on antibiotic prophylaxis in surgery, none of the studies focuses on arthroplasty. Therefore, no publication can be included in the presented health-economic evaluation.

**Ethical, social and legal aspects**
The systematic literature search yields 20 hits. None of the publications explicitly deals with ethical, social or legal aspects of the use of interventions to prevent infections in knee arthroplasty.

**Discussion**

**Methodical aspects**
From a methodological point of view different aspects of the literature search, information sources (studies, systematic reviews of the studies, endoprostheses registers) as well as the information synthesis from these data sources play an important role in the interpretation of the results.

**Hygiene interventions**
Even though the data on most hygiene interventions have been derived from studies for different clinical indications (usually no knee arthroplasty), these results can generally be transferred to knee replacement operations. The evidence level and therefore the validity of the results from non-RCT for the use of these interventions in knee arthroplasty is low, as well as the conclusiveness of the evidence from studies for clinically non-relevant end-points.

The dilemma arises since the conduction of RCT on already established hygiene interventions is ethically problematic, especially because these RCT should include many persons to be able to identify expected small effects.
Antibiotic prophylaxis

Direct evidence for the use of the intravenous antibiotics in knee arthroplasty from RCT and/or endoprostheses registers is missing. The question arises whether the evidence determined on the basis of RCT for hip arthroplasty is valid (i.e., influenced by possible biases) and whether this evidence is transferable on knee replacement operations. With some uncertainty (hip arthroplasty is not the subject of the presented report) it can be assumed that the results for intravenous antibiotic prophylaxis in hip arthroplasty are valid and generally transferable to knee arthroplasty.

Direct evidence is absent for the use of antibiotic in cement in addition to intravenous prophylaxis in operating rooms with clean-air measures on a high level of evidence. However due to the evidence from RCT for operating rooms without clean-air measures and consistency of this evidence with the significant data from the endoprostheses registers it can be assumed that this intervention is effective.

The preoperative decolonization and decontamination of methicillin-resistant staphylococcus aureus positive patients is recommended based on “rational considerations” (expert opinion) regardless of the available literature data.

Conclusions

As no evidence for the effectiveness of hygiene interventions as well as for intravenous antibiotic prophylaxis with a high evidence level has been derived in the presented report, no proposal can be made to change the recommendations of the RKI. No recommendations for the selection of certain antibiotics as well as for the use of the mupirocin nasal ointment can be derived from the existing data. In the operating rooms without clean-air measures, antibiotics in cement should be used additionally to intravenous prophylaxis. In the operating room with clean-air measures the use of antibiotics in cement is also generally recommended until more conclusive data is published. Well-designed studies for different interventions to prevent infections after the knee arthroplasty are missing.

No conclusions from the presented data can be derived concerning the cost-effectiveness of different interventions to prevent infections after knee arthroplasty. Appropriate health-economic studies should be conducted to clarify this issue.

There are no signs for concern about any ethical, social and/or legal consequences in the use of interventions to prevent infections in knee arthroplasty. The independence and the privacy of the patients should be restricted as little as possible. The access to interventions for preventing infections should be equally guaranteed for different social groups. The informed consent of the patients concerning the use of different interventions to prevent infections should also be documented.