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Empiric antibiotic treatment for periprosthetic joint infections: a national survey in The Netherlands

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Early periprosthetic joint infection (PJI) is generally treated by means of debridement, antibiotics and implant retention (DAIR). Subsequently, empiric antibiotic therapy is commenced directly after surgery which is important for the successful treatment of PJI. The aim of this study is to evaluate current nationwide empiric antibiotic treatment regimens for PJI in the Netherlands. An electronic 15-question survey addressing the empiric antibiotic treatment strategy for PJI following THA or TKA was sent to orthopaedic surgeons in all Dutch hospitals in April 2019.

Orthopaedic surgeons active in every single Dutch orthopaedic hospital (n=69) were approached. At least one surgeon in every hospital completed the survey (100% response rate). A protocol dictating the empiric antibiotic treatment following DAIR was used in 87% (60 hospitals). Among all hospitals, 72% (50 hospitals) used antibiotic monotherapy and 28% (19 hospitals) used combination therapy. Cefazolin was the most commonly used regimen in centres opting for monotherapy (42%, 29 hospitals). Similar regimens were used for the empiric treatment of suspected early PJI after revision surgery and for acute hematogenous PJI. In septic patients, combination therapy was preferred (64%). 81% (56 hospitals) incubated tissue biopsies for a minimum of 10 days whereas 16% (9 hospitals) indicated an incubation period of 7 days or less. Even in a small country such as the Netherlands there seems to be no uniformity regarding empiric antibiotic treatment for PJI. Increased uniformity regarding empiric treatment could be an important first step in improving PJI treatment.

Keywords: Periprosthetic joint infection, arthroplasty, antibiotics, empiric treatment, DAIR.

INTRODUCTION

Periprosthetic joint infection (PJI) is one of the most serious complications following total knee or hip arthroplasty (TKA/THA) and accounts for up to 25% of failed TKAs and 15% of failed THAs[1,2]. The number of THA's and TKA's performed per year are projected to increase substantially which will lead to a higher absolute number of cases with PJI[3].

Treatment of PJI can be performed through several different surgical strategies, depending mainly on the timing in onset of symptoms. PJI can be subdivided into early (<3 months after surgery), delayed (3-24) months after surgery) and late (>24 months after surgery) infection[4]. Early PJI (<3 months after surgery) is the most frequently en-countered subtype and is generally treated by means of debridement, antibiotics and implant retention (DAIR)[5,6].

Following DAIR, empiric antibiotic therapy is generally started directly after surgery while awaiting the results of the intra-operative tissue cultures. The latter can take up to 14 days in the presence of low-virulent micro-organisms. However, low virulent pathogens are usually associated with delayed presentation since early acute PJI tends to be caused by virulent pathogens. Adequate early antibiotic treatment is important for the successful treatment of PJI, since rapid exposure of the causative pathogen to an adequate antibiotic agent minimizes chances for biofilm formation and may contribute to treatment success[7]. This has been emphasized by two studies that demonstrated an association between ineffective empiric antibiotic therapy and treatment failure[7,8].

Evidently, empiric antibiotic treatment following DAIR for suspected early PJI should be aimed at the organisms most likely to cause PJI[9] which should be dictated by evidence based protocolized care. The latter minimizes the risk for error[10]. However, existing literature describing the microbiology and the corresponding microbial susceptibility in early

PJI is limited and often of older date[11-14]. The optimal choice of empiric therapy is further complicated by regional differences in causative pathogens and antibiotic susceptibility[15]. For example, the incidence of methicillin resistant *Staphylococcus aureus* (MRSA) is low in the Netherlands, which might render the American recommendation for vancomycin questionable in this region[16].

The development of universal evidence-based guidelines describing the empiric treatment of suspected early PJI following DAIR is therefore difficult. Still, this should not refrain us from attempting to formulate treatment protocols for PJI. Apart from the previously mentioned reduced risk for incorrect treatment, widespread guideline adherence allows for a more effective and faster comparison of outcome data within and across centres[17]. Considering the large variations in reported PJI treatment success rates, there is a pressing need to eliminate avoidable variation in outcomes which arises from differing approaches[17].

In an attempt to identify regional PJI treatment strategies and the presence of treatment protocols, the aim of this study was to evaluate current differences in empiric antibiotic treatment and the usage of protocols following DAIR for suspected PJI across a small European country (the Netherlands).

MATERIALS & METHODS

An electronic 15-questions survey concerning the empiric antibiotic treatment strategy after DAIR for suspected early PJI (<3 months of implantation) and acute hematogenous PJI (separately) was formulated (Figure S1). Subsequently, a list of all orthopaedic

General

1. *Is there a protocol in your clinic regarding empiric antibiotic treatment after DAIR in the event of a suspected PJI?*

Primary THA/TKA

2. *Does empiric antibiotic therapy after DAIR (in a non-septic patient) due to suspected early PJI consist of mono- or combination therapy?*
3. *Which antibiotics are started after DAIR due to suspected early PJI (in a non-septic patient)?*

Revision THA/TKA

4. *The empiric treatment in the event of a suspicion of early PJI differs from the above if there is a status after revision surgery.*
5. *Does empiric antibiotic therapy after DAIR consist of suspected early PJI after revision THA/TKA consist of mono- or combination therapy?*
6. *Which antibiotics are started after DAIR due to suspicion of early PJI after revision THA / TKA?*

Septic Patients

7. *Is the empiric treatment of early PJI after DAIR different in the case of sepsis?*
8. *Does empiric antibiotic therapy after DAIR with suspicion of early PJI in sepsis consist of mono- or combination therapy?*
9. *Which antibiotics are started after DAIR due to suspicion of early PJI with sepsis?*

Acute hematogenous PJI

10. *Does the empiric treatment for suspected early PJI differ from the empiric treatment for acute hematogenous infections?*
11. *Does empiric antibiotic therapy after DAIR for suspected acute hematogenous PJI consist of mono- or combination therapy?*
12. *Which empiric antibiotics are started after DAIR when acute hematogenous PJI is suspected?*

Tissue cultures

13. *How many days are tissue samples incubated until the culture result is considered definitive?*
14. *Are empiric antibiotics discontinued in case of provisional negative results?*
15. *Is antibiotic treatment adjusted based on provisional positive culture results?*

Figure S1. — 15-Question survey.

centres performing THA and/or TKA in the Netherlands was obtained from the National Registry of Orthopaedic Implants (Landelijke Registratie Orthopedische Implantaten, LROI) annual report of 2014. The list was checked for any changes regarding the list's composition that had occurred after 2014. Private practices were excluded from this study. The survey was then sent to all members of the Dutch Hip Society (DHS) and the Dutch Knee Society (DKS) in April 2019. Institutions were contacted by telephone if none of the surgeons active there had responded after two weeks to ensure an optimal response rate and to verify the corresponding surgeons affinity with PJI following THA or TKA. Odd responses were verified by consulting the local treatment protocol of the corresponding hospital (if available). Data analysis was performed using SPSS© version 25.

RESULTS

At least one orthopaedic surgeon involved in the treatment of PJI from every single approached hospital completed the survey (n=69, 100%) of whom 7 (10%) were practicing in academic and 62 (90%) in general hospitals. A protocol with empiric antibiotic regimen following DAIR was established in 60 (87%) hospitals. The 9 hospitals (13%) in which the orthopaedic surgeon was not aware of a treatment protocol were all smaller hospitals.

Antibiotic regimen following DAIR for suspected early PJI within 3 months after primary THA/TKA for suspected early PJI

Among all hospitals, 72% (50 hospitals) used antibiotic monotherapy for suspected early PJI after primary THA/TKA. In general, Cefazolin was most widely used (42%, 29 hospitals), mostly as monotherapy (38%, 26 hospitals) (figure 1). Cephalosporins were the most frequently administered antibiotic class in hospitals using monotherapy, with cefazolin and cefuroxime being used in equal frequencies (both were used in 19% (13 hospitals) each). Rifampicin or aminoglycosides were never used as monotherapy, but rifampicin (21%, 14 hospitals) and aminoglycosides (7%, 5 hospitals) were frequently implemented in empiric combination therapy.

Antibiotic regimen following DAIR for suspected early PJI within 3 months after revision THA/TKA for suspected early PJI

In 93% (64 hospitals), empiric antibiotic treatment for suspected early PJI after revision THA/TKA was identical to the empiric treatment after primary THA/TKA. Monotherapy after revision THA/TKA was used in 72% (50 hospitals). Similar to primary surgery, flucloxacillin (35%, 24 hospitals) and cephalosporins (48%, 33 hospitals) were most often implemented.

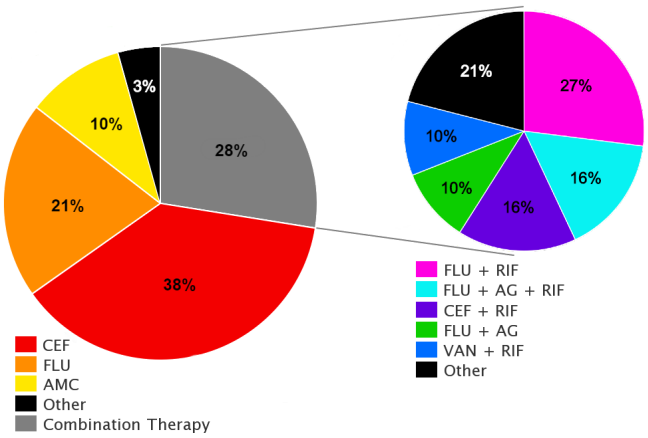

Figure 1. — Empiric antibiotic regimens for suspected early periprosthetic joint infection following primary total joint arthroplasty. Other monotherapeutic regimens include vancomycin (1%), clindamycin (1%) and a case-dependent choice (1%).
FLU: flucloxacillin; CEF: cephalosporin; AMC: amoxicillin-clavulanic acid; RIF: rifampicin; VAN: vancomycin; AG: aminoglycoside; CLI: clindamycin.

Septic patients and acute hematogenous PJI

In septic patients, combination therapy was most frequently used (64%, 44 hospitals), which consisted in most cases of the original empiric treatment regimen plus an aminoglycoside (28%, 19 hospitals). Seven percent of (5 hospitals) added vancomycin to the original monotherapy.

For acute hematogenous PJI no major differences from early PJI were identified (29% combination therapy).

Influence of tissue culture results on antibiotic therapy

81% (56 hospitals) incubated the intraoperatively obtained tissue biopsies for a minimum of 10 days whereas 13% (9 hospitals) incubated the tissue biopsies for 7 days and two (3%) for less than 7 days (figure S1).

Sixty-eight percent (47 hospitals) stopped empiric treatment only after definitive negative results are obtained and no other reasons to continue treatment exist (e.g. absence of clear signs of infection and no pre-operative antibiotic use which could have influenced culture results). Twelve percent (8 hospitals) considered termination of empiric treatment if there are no positive provisional culture results after 4 to 5

days of incubation, 7% (5 hospitals) after 6 to 7 days of incubation, 3% (2 hospitals) after 8 to 10 days of incubation and 10% (7 hospitals) after 10 to 14 days of incubation.

DISCUSSION

A large variation regarding the empiric antibiotic regimen in the treatment of PJI was reported by orthopaedic surgeons in the Netherlands. Orthopaedic surgeons were aware of a local empiric antibiotic treatment protocol following DAIR in 60 (87%) hospitals. 50 hospitals (72%) used combination therapy whereas (28%) used monotherapy for suspected early PJI after primary TKA or THA. Rifampicin was part of combination therapy in 14 (20%) hospitals.

Flucloxacillin was the most frequently used antibiotic with 26 hospitals (38%) using this antibiotic either as monotherapy or as part of a combination therapy for suspected PJI following primary THA/TKA. Only 6% (4 hospitals) did not incorporate a beta-lactam in their empiric regimen. For the most part, empiric treatment for suspected early PJI after revision THA/TKA was not different from previously mentioned empiric treatment (93%).

A majority (68%, 47 hospitals) continued empiric treatment until tissue cultures were definitively negative which could take up to 14 days.

The finding that 13% of Dutch hospitals lack the awareness or presence of treatment protocols regarding PJI seems worrying. A lack of treatment protocols (or awareness of them) predisposes to errors[10] and hinders more effective and faster comparison of outcome data within and across hospitals[17]. Despite the latter, all orthopaedic surgeons reported on the local preference regarding empiric antibiotic treatment for PJI which demonstrated a large variety. This reported variety in empiric treatment is remarkable since the Netherlands only covers a relatively small area (41.543 km² with a population of 17.4 million people). Formulation of more uniform treatment guidelines therefore seems like a viable first step in laying the foundation for further research on the optimal treatment of PJI.

In order to formulate adequate regional treatment protocols, institutions should elucidate the local spectrum of pathogens and their corresponding antimicrobial susceptibility. Accumulation of this data could contribute to the formulation of optimal regional protocols dictating empiric antibiotic treatment which may, in turn, improve treatment success rates.

However, high antibiotic coverage of the identified spectrum of pathogens does not necessarily equal high efficacy since antibiotic activity can be reduced by implant-associated biofilms[18]. For example, the activity of glycopeptides was reduced in *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms[19-23]. In contrast, some other antibiotics including flucloxacillin and cefazolin were not affected by *Staphylococcus epidermidis* biofilm[22-23]. The latter might be one of the reasons for the popularity of flucloxacillin usage in the empiric treatment of PJI in the Netherlands.

This study shows that rifampicin is used as part of empiric combination therapy in 14 (20%) hospitals. In contrast, most hospitals specifically reserve rifampicin for *Staphylococcus* infections only and start it 3-5 days after DAIR and only when wound drainage has stopped to reduce the (potential) development of resistance of the causative pathogens[24,25]. In early PJI, the bacterial load is probably still high following DAIR, and further reduction of the load is accomplished by antibiotic use in the first 3-5 days[24]. A reduced load reduces the risk of development of rifampicin resistance. In addition rifampicin can induce resistance in staphylococci of the skin microbiome[26], which might lead to exogenous super-infection by rifampicin-resistant staphylococci. This risk is reduced when rifampicin is withheld until wound drainage has stopped. On the other hand, early treatment with rifampicin may prevent (additional) bacterial adhesion to the implant and early biofilm formation[27,28]. Unfortunately, there are no trials investigating the clinical outcome of early versus late start of rifampicin.

Timely termination of empiric antibiotics in selected cases in the absence of confirmed PJI could potentially reduce the costs associated with unnecessary administration of antibiotics, decrease the emergence of resistant organisms, and reduce the risk of potential side effects related to antibiotic toxicity. The time to positive tissue cultures very rarely exceeds 5 days[12], except for *Cutibacterium acnes*. However, only 12% of hospitals consider termination or change of empiric treatment to specifically cover *Cutibacterium acnes* after 5 days of incubation.

LIMITATIONS

The most important limitation is that this study reflects only a single small country (the Netherlands), and therefore our recommendations do not necessarily apply to other nations throughout the world. Additional limitations include that only a single surgeon was approached, which may not reflect the opinion of the whole (orthopaedic) team in the concerned clinic.

CONCLUSION

Empiric antibiotic treatment for PJIs varies significantly throughout the Netherlands and, remarkably, orthopaedic surgeons in 13% of hospitals lack (awareness of) a protocol regarding empiric antibiotic treatment. This leaves room for improvement in the treatment of PJI through the formulation of uniform treatment protocols which should be based on the regional epidemiology of causative pathogens and antimicrobial susceptibilities. These protocols should reduce the risk for incorrect treatment and will allow for a more effective and faster comparison of treatment outcomes.

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