2023 exceptional surveillance of Myeloma (NICE guideline NG35)

Surveillance proposal

We propose to not update section 1.8 of the guideline on Myeloma (NICE guideline NG35).

Following publication of the TEAMM trial in 2019, and a meta analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma (2019) (including three RCTs, one of which is the TEAMM trial), there remains uncertainty about the effectiveness or safety of antibiotic prophylaxis to reduce febrile episodes and death in patients with newly diagnosed myeloma.

Conflicting topic expert feedback on the impact of the TEAMM trial reflects this uncertainty as only two out of three topic experts stated that the TEAMM trial provided sufficient evidence to update the Myeloma guideline (NG35 section 1.8). There were also inconsistencies in the current use of antibiotics in patients with newly diagnosed myeloma across centers. Two topic experts are already including antibiotic prophylaxis in practice in their centers, while one is not. This topic expert also raised concerns around antimicrobial resistance if antibiotic prophylaxis became standard practice.

Reason for the exceptional review

The reason for this exceptional review is to examine the impact of the publication of the TEAMM trial (2019) and the meta analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma (2019) on section 1.8 of the Myeloma guideline (NICE guideline NG35).

In May 2020, we were notified about the publication of the TEAMM trial and its potential impact on NG35. The myeloma guideline has a section on preventing infection (section 1.8) but does not currently recommend

prophylactic antibiotics (or advise against them) as at the time of guideline development the evidence was too weak to develop recommendations. The publication of the TEAMM trial in 2019 is the first large trial in this area that may have an impact on the use of antibiotic prophylaxis for people with myeloma undergoing initial treatment.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review (TEAMM trial), and evidence submitted by topic experts (a meta analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma).
- Feedback from topic experts.
- Considering the evidence used to develop the guideline in 2016.
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

We asked topic experts if they were aware of any additional, new or ongoing trials involving prophylactic antibiotics, and they identified a meta analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma (2019).

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

New evidence for the effectiveness or safety of antibiotic prophylaxis to reduce febrile episodes and death in patients with newly diagnosed myeloma.

Two studies were identified: 1 RCT and 1 meta-analysis. The study abstracts from PubMed are below (italics) and linked to from this document. A commentary assessing the impact of each study on section 1.8 of the Myeloma guideline (NICE guideline NG35) follows each abstract.

Study 1

Drayson M T, et al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol. 2019 Dec; 20(12):1760-1772. doi: 10.1016/S1470-2045(19)30506-6. Epub 2019 Oct 23.

Background: *Myeloma causes profound immunodeficiency and recurrent, serious infections. Around 5500 new cases of myeloma are diagnosed per year in the UK, and a quarter of patients will have a serious infection within 3 months of diagnosis. We aimed to assess whether patients newly diagnosed with myeloma benefit from antibiotic prophylaxis to prevent infection, and to investigate the effect on antibiotic-resistant organism carriage and health care-associated infections in patients with newly diagnosed myeloma.*

Methods: *TEAMM was a prospective, multicentre, double-blind, placebo-controlled randomised trial in patients aged 21 years and older with newly diagnosed myeloma in 93 UK hospitals. All enrolled patients were within 14 days of starting active myeloma treatment. We randomly assigned patients (1:1) to levofloxacin or placebo with a computerised minimisation algorithm. Allocation was stratified by centre, estimated glomerular filtration rate, and intention to proceed to high-dose chemotherapy with autologous stem cell transplantation. All investigators, patients, laboratory, and trial co-ordination staff were masked to the treatment allocation. Patients were given 500 mg of levofloxacin (two 250 mg tablets), orally once daily for 12 weeks, or placebo*

tablets (two tablets, orally once daily for 12 weeks), with dose reduction according to estimated glomerular filtration rate every 4 weeks. Follow-up visits occurred every 4 weeks up to week 16, and at 1 year. The primary outcome was time to first febrile episode or death from all causes within the first 12 weeks of trial treatment. All randomised patients were included in an intention-to-treat analysis of the primary endpoint. This study is registered with the ISRCTN registry, number ISRCTN51731976, and the EU Clinical Trials Register, number 2011-000366-35.

Findings: *Between Aug 15, 2012, and April 29, 2016, we enrolled and randomly assigned 977 patients to receive levofloxacin prophylaxis (489 patients) or placebo (488 patients). Median follow-up was 12 months (IQR 8-13). 95 (19%) first febrile episodes or deaths occurred in 489 patients in the levofloxacin group versus 134 (27%) in 488 patients in the placebo group (hazard ratio 0·66, 95% CI 0·51-0·86; p=0·0018. 597 serious adverse events were reported up to 16 weeks from the start of trial treatment (308 [52%] of which were in the levofloxacin group and 289 [48%] of which were in the placebo group). Serious adverse events were similar between the two groups except for five episodes (1%) of mostly reversible tendonitis in the levofloxacin group.*

Interpretation: *Addition of prophylactic levofloxacin to active myeloma treatment during the first 12 weeks of therapy significantly reduced febrile episodes and deaths compared with placebo without increasing health care-associated infections. These results suggest that prophylactic levofloxacin could be used for patients with newly diagnosed myeloma undergoing anti-myeloma therapy.*

Assessment of the impact on section 1.8 of the Myeloma guideline (NICE guideline NG35): The TEAMM trial is a prospective, multicentre, double-blind, placebo-controlled randomised trial of antibiotic prophylaxis in patients with myeloma. It is the first trial of this size and design to show that prophylactic levofloxacin could be used for newly diagnosed myeloma patients undergoing the first 12 weeks of anti-myeloma therapy, to reduce febrile episodes and

deaths compared with placebo without increasing health care-associated infections. The trial was designed to map onto current standard practice in the UK.

A limitation of the study is that the patient population recruited were generally younger and had fewer co-morbidities than likely 'real-world' patients, leading to a small total number of deaths. The authors also report that there may be additional mechanisms underlying the benefits of levofloxacin prophylaxis other than a reduction in infection. For example, a change in the microbiome might have contributed to a reduction in inflammation. Further in-depth studies on the microbiome are needed to evaluate this.

A further limitation was the high number of withdrawals, despite the low toxicity of levofloxacin. Around half of the withdrawals occurred in the first 4 weeks. Patients had to collect stool samples every 4 weeks, take their temperatures daily, and fill in a diary, which might have been burdensome. Forty percent of patients were also in a trial of active therapy (Myeloma XI) which may have been prioritised over the TEAMM trial and been another reason for withdrawal. It is important to note that the patient population was 91% white, suggesting further research should be done with individuals from different ethnicity background.

This RCT provides some good quality evidence on the effectiveness and safety of antibiotic prophylaxis, with levofloxacin, to reduce febrile episodes and death in patients with newly diagnosed myeloma. However, uncertainty remains around whether it would be more appropriate to wait until a patient has an infection before prescribing antibiotics due to concerns around side effects and antibiotic resistance. The use of levofloxacin prophylaxis for periods greater than 12 weeks also needs to be explored in future trials. It is unclear whether this single RCT provides sufficient evidence to warrant an update to section 1.8 of the Myeloma guideline (NICE guideline NG35).

Study 2

Mohyuddin GR, et al. Antibiotic prophylaxis for patients with newly diagnosed multiple myeloma: Systematic review and meta-analysis. European journal of heamatology. 2019 Dec 104(5): 420-426. doi.org/10.1111/ejh.13374

Objective: *Ascertain the benefit of prophylactic antibiotics for patients with newly diagnosed multiple myeloma (MM), given that clinical trials evaluating this have had conflicting results.*

Methods: *We performed a systematic review and meta-analysis evaluating the use of prophylactic antibiotics in patients with MM and its impact on infection risk and mortality.*

Results: *Across three included studies, a total of 664 patients received antibiotics and 650 patients received no antibiotics. The overall incidence of infection within 3 months was lower for antibiotic group compared to placebo (18.4% vs 23.4%, RR: 0.79, 95% CI 0.62-1.00, P = .05, I^2 = 6.5%). There was no difference in mortality in the first 3 months (1.5% vs 3.5%, RR: 0.47, 95% CI 0.17-1.27, P = .60, I^2 = 28.1%).*

Conclusion: *Antibiotic prophylaxis for a finite duration can decrease the overall incidence of infection within the first 3 months following diagnosis. This does not lead to a decrease in mortality. Further data on antibiotic resistance patterns, toxicity, healthcare expenditures, and the impact of antibiotics on subsequent therapies can assist providers in helping make decisions on prophylactic antibiotics with their patients.*

Assessment of the impact on section 1.8 of the Myeloma guideline (NICE guideline NG35): This is the first meta-analysis to evaluate the impact of prophylactic antibiotics in myeloma patients in decreasing the risk of infection and mortality. The results indicate that antibiotic prophylaxis for 2-3 months following diagnosis leads to a decrease in the incidence of infections for patients with myeloma. However, this decrease was just at the threshold of statistical significance. Furthermore, there was no decrease in mortality noted

and it is unknown if the incidence of complications may increase if prophylaxis was extended for a longer period than 3 months.

There was considerable variability in findings across the three RCTs included in this meta-analysis, which led to heterogeneity in the results. The meta-analysis consists of stwo small randomized controlled trials (Oken et al, 54 patients and Vesole et al, 212 patients), which were included in the original Myeloma guideline in 2016 (NICE guideline NG35), and a third larger, double blind randomized, placebo-controlled trial (TEAMM trial, 977 patients).

The results of the TEAMM trial differs significantly from Vesole et al. Vesole et al reported negative results with no significant impact on infection overall while the TEAMM trial found that levofloxacin prophylaxis led to a reduction in febrile episodes and death at 12 weeks. However, a comparison of the populations in the two studies was not possible due to differences in their primary endpoints and selective reporting of variables. The duration of antibiotics differed with 2 months used in Vesole et al and 3 months in the TEAMM trial, and the data in Vesole et al may not be applicable to today's patient population which rarely receives cytotoxic chemotherapy. Vesole et al also did not report on toxicities resulting from antibiotic use. Furthermore, local antibiotic resistance patterns in the UK and United States may also play a significant role in the results.

Another point to consider is that there is increasing evidence that the gut microbiome is an important determinant in patients' response to immunotherapy. Given that immunotherapy may be a current treatment option for people with relapsed myeloma, caution is needed when considering antibiotic prophylaxis, as the impact this may have on subsequent immunotherapies is unknown.

The heterogeneity of the studies is an important limitation of this meta-analysis. Further research is needed on antibiotic resistance, toxicity, mortality, healthcare expenditures, and the impact of antibiotics on subsequent therapies. This meta-analysis therefore does not provide sufficient

evidence to warrant an update to section 1.8 of the Myeloma guideline (NICE guideline NG35).

Topic expert feedback

Five topic experts were contacted by email (three Consultant Haematologists; a Consultant Clinical Oncologist; and a Haematology Advanced Nurse Practitioner) and asked to complete a survey.

We received responses from 3 topic experts (two Consultant Haematologists and a Consultant Clinical Oncologist). Out of the two remaining individuals, one topic expert was on maternity leave and the other gave no response.

Two out of the three topic experts stated that the TEAMM trial provided sufficient evidence to update the Myeloma guideline (NG35 section 1.8). These Consultant Haematologists highlighted that the risk of bacterial infections is affecting morbidity and mortality, particularly at initiation of treatment in all newly diagnosed patients. The topic experts reported that the study recommendations are already in practice in their centers as all newly diagnosed patients receive Levofloxacin prophylaxis for 12 weeks. They had no concerns about antimicrobial resistance. It is important to note that one of these topic experts works with an author on the TEAMM trial.

The third topic expert (a Consultant Clinical Oncologist) did not believe that the TEAMM trial provides sufficient evidence to trigger an update to the Myeloma guideline (NG35 section 1.8). This topic expert reported that they did not currently give Levofloxacin prophylaxis to newly diagnosed patients and they raised concerns around antimicrobial resistance if this became standard practice.

None of the topic experts were aware of any additional new or ongoing RCTs. One topic expert highlighted that the meta analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma had been published in 2019. This meta analysis included the TEAMM trial and two small RCTs (Oken et al 1996 and Vesole et al 2012).

Information considered when developing the guideline

During the development of the guideline in 2016 the committee concluded that there was insufficient evidence on prophylactic antibiotics. Therefore, the myeloma guideline has a section on preventing infection (section 1.8) but does not currently recommend prophylactic antibiotics (or advise against them). There were no recommendations for research on this topic.

The scope when developing the 2016 guideline was: What is the most effective prophylactic strategy for infection in patients with myeloma (including immunoglobulin, antibiotics, growth factors and vaccinations)? The review included 4 systematic reviews, 5 randomised trials and 2 non randomised comparative studies. The only evidence for antibiotics came from 2 RCTs. These RCTs (Oken et al, 1996 and Vesole et al, 2012) are included in the meta analysis in this exceptional review.

The first low quality RCT (n=54 patients) compared 2 months of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis with no prophylaxis in patients with myeloma (Oken et al, 1996). Low quality evidence suggested that TMP-SMZ prophylaxis is effective compared to no prophylaxis in reducing the rate of infection (18% versus 46% respectively; RR 0.39; 95% CI 0.16 to 0.95).

Low quality evidence from the second RCT included 212 patients with newly diagnosed myeloma (Vesole et al, 2012). This found uncertainty around the effectiveness of prophylactic antibiotics (quinolone/ofloxacin or trimethoprim-sulfamethoxazole) compared to observation alone. The rate of severe bacterial infection was 9.3% with antibiotics versus 15.9% with observation (RR=0.59; 95% C.I. 0.28 to 1.28)

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

The evidence base on this topic is not conclusive. The TEAMM trial is the first large RCT to show that prophylactic levofloxacin could be used for newly diagnosed myeloma patients undergoing the first 12 weeks of anti-myeloma therapy, to reduce febrile episodes and deaths compared with placebo. However, uncertainty remains whether this single RCT provides sufficient evidence to warrant an update to section 1.8 of the Myeloma guideline (NICE guideline NG35). Concerns are raised around side effects and antibiotic resistance and the use of levofloxacin prophylaxis for periods greater than 12 weeks also needs to be explored in future trials.

A meta-analysis to evaluate the impact of prophylactic antibiotics in myeloma patients also indicates that antibiotic prophylaxis following a diagnosis of myeloma leads to a decrease in the incidence of infections. However, this decrease was just at the threshold of statistical significance. Furthermore, there was no decrease in mortality, and it is unknown if the incidence of complications may increase if prophylaxis was extended for a longer period than 3 months.

The topic experts highlight a variation in current practice, with some centers already giving newly diagnosed patients levofloxacin prophylaxis for 12 weeks as recommended by the TEAMM trial. Other centers are not currently giving levofloxacin prophylaxis to newly diagnosed patients as concerns are raised around antimicrobial resistance if this became standard practice.

Due to the insufficient evidence and inconsistencies in the topic expert feedback, we propose to not update the guideline on Myeloma (NICE guideline NG35).