NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2023 surveillance of Myeloma: diagnosis and management (2016)

Consultation dates: 27th April to 12th May 2023

1. Do you agree with the proposal not to update the section 1.8 of guideline on Myeloma (NICE guideline NG35)? Please could let us know if you agree or disagree (yes/no) and if you disagree can you provide your comments or rationales?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Janssen UK	Yes	Agree. The current section 1.8 has little content that has changed or is controversial. For preventing infection, intravenous immunoglobulin replacement therapy is already recommended for people who have hypogammaglobulinaemia and recurrent infections. With regards to giving Levofloxacin prophylaxis to newly diagnosed patients based on the TEAMM trial and the meta-analysis on antibiotic prophylaxis, the evidence base on this topic is not conclusive.	Thank you for your comments.

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University Hospital of Wales	No	I do not agree and I think the proposal should be updated to include advice recommending the use of antibiotic prophylaxis for newly diagnosed myeloma patients. This would reflect the current standard of care in our centres and across the UK both for patients on trials and not on trials. Myeloma and it's treatment are highly immunosuppressive and the paucity of evidence for its use is just a reflection if this being a niche therapeutic area.	Thank you for your comments and raising awareness that many centres are currently using antibiotic prophylaxis for newly diagnosed myeloma patients without the support of consistent evidence. Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients. There remains uncertainty in the evidence regarding the benefits and harms (e.g. antimicrobial resistance) of antibiotic prophylaxis for newly diagnosed myeloma patients.
UIK Myeloma Society	No	No we feel strongly (the UK Myeloma Society) that the TEAMM trial results are correct and that prophylactic antibiotics should be recommended as per the trial results for patients with multiple myeloma undergoing first line anti-myeloma therapy We feel strongly that the results of the TEAMM trial have not been assessed reasonably at all and judged in an extremely negative light despite this been a phase III randomised double blind placebo trial of approximately 1000 patients Specifically • The TEAMM trial is the largest randomised trial of antibiotic prophylaxis and its results should not be discounted because smaller less well designed and powered studies did not reach exactly the same conclusions. Most centres will have already implemented this as SoC in association with their antibiotic steering committees (or equivalent) indicating haematologists follow the results of this trial	Thank you for your comments. Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients. There remains uncertainty in the evidence regarding the benefits and harms (e.g. antimicrobial resistance) of antibiotic prophylaxis for newly diagnosed myeloma patients. Please see the surveillance report for more information on the limitations of the TEAMM trial. Thank you for highlighting that some centres are currently using antibiotic prophylaxis for newly diagnosed myeloma patients without the support of consistent evidence. Based on topic experts feedback and stakeholders responses from this public consultation, not all centres in the UK are implementing the intervention (i.e. the use of antibiotic prophylaxis for newly diagnosed myeloma patients). This inconsistency across the centres in the UK reflects the uncertainty of the evidence. The

			limitations of the TEAMM trial, as well as the meta-analysis from Mohyuddin et al (2019) are detailed in the surveillance report.
		• NICE assert that the high level of withdrawals from study is a limitation. We would argue the opposite and that even with withdrawals a positive result was achieved which likely makes the case even stronger.	Please note that the high level of withdrawals from the TEAMM trial was highlighted as the main limitation of the study by the authors of the trial. The withdrawal of a participant results in missing data and the potential for attrition bias. This can influence the balance of confounders between study groups as ideally, we want the groups to be as similar as possible, differing only in terms of the intervention they receive. As the reason for these withdrawals are unknown, it was not possible to characterize or statistically address those that have withdrawn to minimize this bias. These dropouts can also influence the statistical power of the study and may inflate positive effect estimates.
		• NICE argues that there is uncertainty as to whether to wait until infections develop – the TEAMM study demonstrates that this approach increases the risk of infection and death/hospital admission and therefore it would make sense to apply the trial results now rather than await a further study.	The uncertainty as to whether to wait until infections develop to provide antibiotic prophylaxis relates to concerns around antimicrobial resistance. NICE recognises that while antibiotic resistance was not specifically investigated in the TEAMM trial, there was no increase in healthcare associated infections. However, the authors of the TEAMM trial highlight that when considering their findings, local antibiotic resistance proportions must be considered. The meta-analysis in the current review also concludes that further data are required on antibiotic resistance patterns. Please note that the meta-analysis also states 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, the authors suggest that caution is needed when considering antibiotics before an infection develops, as the impact this may have on subsequent immunotherapies is

			unknown. Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients
		• NICE argue that there is uncertainty about whether 12 weeks is optimal or potentially longer. That is agreed but there remains a very strong case to offer levofloxacin for 12 weeks.	Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients for 12 weeks. There remains uncertainty in the evidence regarding the benefits and harms (e.g. antimicrobial resistance) of antibiotic prophylaxis for newly diagnosed myeloma patients. Please see the surveillance report for more information on the limitations of the TEAMM trial.
		The haematologist experts who reviewed the data felt that the evidence from TEAMM is strong enough to change their own practice but the clinical oncologist does not. In the UK, clinical oncologists do not routinely treat myeloma with systemic therapy so will not see in clinical practice the benefit of reduction in infections. They cannot extrapolate their experience from solid tumours as myeloma causes a profound secondary immunodeficiency not seen with solid tumours. The methodology for the 'expert review' is not adequate with only 3 responses, no expert input requested from micro/ anti-infective colleagues and no pharmacist involved. Antibiotic stewardship in practice has heavy pharmacy influence and a pharmacist should be included.	Stakeholder responses show that not all hematologists are implementing the intervention due to concerns around antimicrobial resistance. In terms of the methodology for the expert review, there have been two rounds of requests to invite topic experts to feedback on the current review. This public consultation also adds to the expert input. Recommendations on antibiotic stewardship can be found in the NICE Antimicrobial stewardship guideline (NG15).
		• The conclusion that "after a review of this section no change is required" could be misleading (they should be specific in terms of the review/ feedback).	It is unclear where the statement "after a review of this section no change is required" is included in the current review. The overall discussion section provides details about why the evidence base on this topic is not conclusive.

		We also feel that this section should be broader. We are seeing a significant infection risk in patients with multiple relapsed disease and strong consideration should be given to antibiotic prophylaxis in later lines of therapy and better management of secondary immunodeficiency. This is standard practice now in the UK in most units. Serious infections are an increasing problem with novel agents such as BITE antibodies and CAR T cell therapy. There may also be individual patients requiring antifungal prophylaxis and pneumocystis jirovecii prophylaxis	Thank you for your feedback on infection risk. The current review was triggered by the submission of key evidence that relates to preventing infections in Myeloma (recommendations 1.8.1 to 1.8.6).
University Hospital Southampton	No	No. We do not feel that the evidence review accurately reflects the TEAMM trial evidence which met its primary endpoint in terms of reduction in deaths and hospitalisations with the use of prophylactic levofloxacin. The expert evidence review seems to have been misinterpreted as the two haematologists who treat myeloma follow the evidence whereas the only expert who disagreed is a clinical oncologist who will not be treating myeloma with systemic therapy. This does not appear to have been taken in to account in weighing up the opinion. We feel that a formal review with appropriate expert clinical input would be appropriate.	Thank you for your comments. The current review found the evidence presented within the TEAMM trial (2019) and the meta-analysis on antibiotic prophylaxis for patients with newly diagnosed multiple myeloma (2019), which includes the TEAMM trial, to be inconclusive. The outcome is biased due to a number of patient withdrawals which inflated the positive effect. Please see surveillance report for the limitations of these 2 studies. Due to these limitations, uncertainty remains whether there are sufficient evidence to warrant an update. Thank you for highlighting that the two haematologist topic experts reported that they are currently using antibiotic prophylaxis for newly diagnosed myeloma patients in their centres. However, this does not mean that all UK centres are currently implementing antibiotic prophylaxis. Topic expert and stakeholder feedback highlights variation in practice, with some UK centres not implementing the results of the TEAMM trial due to concerns around antimicrobial resistance. This inconsistency in implementation reflects the uncertainty of the evidence.

Haematology MDT based at St Helens & Knowsley Teaching Hospitals combined with Warrington and Halton and Southport & Ormskirk Hospitals	Yes	Yes, we agree with not updating. There is no clinically relevant outcome benefit in using prophylactic antibiotics that justifies the exposure to prolonged antibiotics and risk of antibiotic resistance.	Thank you for your comments.
Myeloma UK	No	We do not agree with the proposal not to update the section 1.8 of the NG35 guidelines. The evidence from the TEAMM trial and the meta-analysis demonstrate that antibiotic prophylaxis is statistically beneficial in reducing infections. The consultation proposal confirms the safety and efficacy of antibiotic prophylaxis to the extent that the two specialist clinical consultants in haematology have recommended a change to NG35 Section 1.8. Further, they have already implemented the routine use of antibiotic prophylaxis in their respective clinical practise. We believe that the weighting of their expert opinion should be considered. We feel the guideline should be updated using the evidence base of current data, whilst we note the] requirement for further data to address the potential for	Thank you for your comments. NICE agrees that the evidence from the TEAMM found that antibiotic prophylaxis is statistically beneficial in reducing infections at 12 weeks. However, although the meta-analysis found that that antibiotic prophylaxis following a diagnosis of myeloma leads to a decrease in the incidence of infections, this decrease was just at the threshold of statistical significance. Furthermore, there was no decrease in mortality. The inconsistencies and paucity of data mean that NICE proposes to not update the guideline at this time. Thank you for highlighting that the two haematologist topic experts reported that they are currently using antibiotic prophylaxis for newly diagnosed myeloma patients in their centres. However, there are other UK centres who are not implementing the intervention due to concerns around antimicrobial resistance (e.g. stakeholders from this public consultation). This inconsistency in implementation reflects the uncertainty of the evidence. Thank you for your comment. Although there was no increase in health care-associated infections in the levofloxacin arm in the TEAMM trail when compared to the placebo arm, the authors highlight that when considering their findings, local antibiotic

		antimicrobial resistance as noted by the oncology consultant reviewer. Of note, the TEAMM study demonstrated no increase in health care-associated infections in the levofloxacin arm compared to placebo suggesting antimicrobial resistance was not of clinical concern in this study.	resistance proportions must be considered. Furthermore, although the meta-analysis found that that antibiotic prophylaxis following a diagnosis of myeloma leads to a decrease in the incidence of infections, this decrease was just at the threshold of statistical significance. There was also no decrease in mortality Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients. There remains uncertainty in the evidence regarding the benefits and harms (e.g. antimicrobial resistance) of antibiotic prophylaxis for newly diagnosed myeloma patients. Please see the surveillance report for more information on the limitations of the TEAMM trial.
		Compared to solid tumour cancer patients, myeloma patients are at higher risk of infection leading to morbidity and mortality. Infection risk is highest within the first three months of diagnosis and is of concern in cases of relapse and severely impaired immunity. Infection is one of the risk factors for early mortality. In this cancer type, we feel that antibiotic prophylaxis has the evidence-base to support optimal health and quality of life outcomes.	Based on NICE's methods and processes, there is currently insufficient evidence for NICE to recommend or not to recommend the use of antibiotic prophylaxis for newly diagnosed myeloma patients. There remains uncertainty in the evidence regarding the benefits and harms (e.g. antimicrobial resistance) of antibiotic prophylaxis for newly diagnosed myeloma patients. Please see the surveillance report for more information on the limitations of the TEAMM trial.
		We also recommend a review of the NG35 guidance to reflect new therapeutic options approved since the publication of the guidance in 2018.	Thank you for raising NICE technology appraisals (TAs) that were approved since the publication of this guideline. NICE recognises the challenge that not having this information in one place poses, and we are looking at how we can fulfil our strategic ambition to rapidly incorporate information on the relative effectiveness of new technologies, medicines, and interventions. The NICE strategy 2021 to 2026 | Corporate publications | Who we are | About | NICE.

		Further, we feel it would be of benefit for NICE to publish the expert review assessment of TEAMM and the meta-analysis detailing the rationale for NICE to propose not updating section 1.8.	The topic expert feedback on the TEAMM trial and meta-analysis is reported in the surveillance review and will be published alongside these responses to consultation.

2. Are you aware of any additional randomised controlled trials (RCTs) (published or ongoing trials) on this topic area?

Stakeholder	Overall response	Comments	NICE response
Janssen UK	No	Janssen UK is not aware of any additional new or ongoing randomised controlled trials on this topic area.	Thank you.
University Hospital of Wales	No	No because most trials recommend following local standard of care in this area rather than testing the question or being prescriptive.	Thank you.
UIK Myeloma Society	No	No. It is incredibly unlikley that anyone would repeat the TEAMM trial as that is accepted by the myeloma community	Thank you.
University Hospital Southampton	No	No	Thank you.
Haematology MDT based at St Helens &	No	No	Thank you.

Knowsley Teaching Hospitals combined with Warrington and Halton and Southport & Ormskirk Hospitals			
Myeloma UK	Yes	The International Myeloma Working Group (IMWG) has published consensus guidelines and recommendations based on available evidence about infection risk and prevention in multiple myeloma (2022). The recommendations include use of prophylaxis levofloxacin (500mg OD) for newly diagnosed patients at intermediate and high risk of infection. Raje NS, Anaissie E, Kumar SK, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. Lancet Haematol. 2022;9(2):143-161. DOI: 1016/S2352-3026(21)00283-0	Thank you for forwarding the reference to The International Myeloma Working Group's (IMWG) consensus guidelines and recommendations. While this paper provides insights on the issues associated with the risk of infection and prevention of infectious complications in multiple myeloma, it does not meet the inclusion criteria of the current review. These guidelines also do not include any additional relevant evidence that has not been considered in this surveillance review.

3. Are you aware of any health inequality issues in this area? If yes, can you provide your comments?

Stakeholder	Overall response	Comments	NICE response
Janssen UK	No	Janssen UK is not aware of any health inequality in this area.	Thank you.

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University Hospital of Wales	Yes	Yes, patients who live in rural areas may live more than an hour from their nearest treatment centre. In cases of febrile neutropenia this delay in presentation could be compounded by a lack of antibiotic prophylaxis.	Thank you for your comment. This potential issue will be recorded in the HEIA.
UIK Myeloma Society	No	Not aware	Thank you
University Hospital Southampton	No	No	Thank you
Haematology MDT based at St Helens & Knowsley Teaching Hospitals combined with Warrington and Halton and Southport & Ormskirk Hospitals	No	No	Thank you
Myeloma UK	Yes	Health inequalities and deprivation indices are correlates of health outcomes for cancer populations*. A report in 2020 cited that 20,000 extra cases of cancer each year in the UK may be attributable to socio and financial deprivation, and survival is worse for the most deprived groups. Health inequalities impact across the cancer patient journey from seeking a healthcare referral to screening, diagnosis, and treatment outcomes.	Thank you for your comment. This potential issue will be added to the HEIA.

		Ethnic minority patients with myeloma have poorer outcomes overall, it is possible that there could be an inequality impact by not considering prophylaxis for at-risk-of-infection patients who may have co-morbidities and may experience more difficulty accessing routine cancer services. *Cancer in the UK 2020: Socio-economic deprivation. Cancer Research UK. Published 30 September 2020.	

4. What is the current practice in your centre/local area? Do you routinely provide antibiotic prophylaxis for people with newly diagnosed myeloma who are starting therapy?

Stakeholder	Overall response	Comments	NICE response
Janssen UK	no	Antibiotic prophylaxis for people with newly diagnosed myeloma who are starting therapy is not standard practice due to concerns around antimicrobial resistance in some centres.	Thank you.
University Hospital of Wales	Yes	Yes we do usually Co-Trimoxazole or Ciprofloxacin for at least 12 weeks.	Thank you.

UIK Myeloma Society	Yes	Yes we all give antibiotic prophylaxis as per TEAMM trial results. It is standard of care	Thank you.
University Hospital Southampton	Yes	Since the publication of the TEAMM trial the myeloma service at University Hospital Southampton has updated its practice to routinely offer levofloxacin prophylaxis for 12 weeks alongside co-trimoxazole.	Thank you.
Haematology MDT based at St Helens & Knowsley Teaching Hospitals combined with Warrington and Halton and Southport & Ormskirk Hospitals	No	No we do not. See first answer above.	Thank you.
Myeloma UK	NA	Not applicable. As per our response in question 1, we note that expert clinical haematologists who provided evidence to the review proposal have already adopted antibiotic prophylaxis in their respective clinics. We recommend an update to section 1.8, including consideration of prophylaxis in later lines of therapy in addition to recently diagnosed patients; with further input from relevant specialists who routinely manage infections in myeloma patients.	Thank you for your comment. Thank you for highlighting that the two haematologist topic experts reported that they are currently using antibiotic prophylaxis for newly diagnosed myeloma patients in their centres. However, there are other UK centres who are not implementing the intervention due to concerns around antimicrobial resistance (e.g., stakeholders from this public consultation). This inconsistency in implementation reflects the uncertainty of the evidence.

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