NICE National Institute for Health and Care Excellence

2020 exceptional surveillance of neutropenic sepsis: prevention and management in people with cancer (NICE guideline CG151)

Surveillance report

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Surveillance decision

We will not update the NICE guideline on neutropenic sepsis.

We will amend recommendation 1.2.1.1 about fluoroquinolones for prophylaxis of neutropenic sepsis to add a link to the Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update on fluoroquinolone antibiotics.

Reasons for the decision

The NICE guideline on neutropenic sepsis recommends offering fluoroquinolones for primary prophylaxis. The guideline committee came to this conclusion after examining over 200 randomised controlled trials of primary prophylaxis, basing their decision on clinical evidence that fluoroquinolones are more effective than placebo for reducing mortality and neutropenic sepsis. Additionally, an economic model built for the guideline showed that primary prophylaxis with fluoroquinolones in solid tumours is more cost effective than other strategies, which was robust to sensitivity analysis. Risks of fluoroquinolones were noted by the committee, such as side effects and bacterial resistance, but it was agreed that the benefit of saving lives outweighed potential harms.

Routine surveillance of the guideline published in February 2019 identified a Cochrane review, which concluded that among all antibiotics examined, the most significant reduction in mortality was with quinolones. The new evidence was consistent with the recommendation to offer fluoroquinolones for prophylaxis.

In March 2019, the MHRA published a Drug Safety Update (DSU) announcing restrictions and precautions for the use of fluoroquinolone antibiotics because of rare reports of disabling and potentially long-lasting or irreversible side effects. However, the DSU also notes that restrictions should not prevent use of a fluoroquinolone for serious or severe infections if this is consistent with UK national guidance, and where the benefit is thought to outweigh the risk. Fluoroquinolone prophylaxis of serious infections, including neutropenic sepsis, is not specifically discussed. An alert about the DSU was added to the landing page of the neutropenic sepsis guideline, but the impact of the DSU on the management of this potentially fatal infection needed to be further explored in an exceptional surveillance review.

The review indicated that fluoroquinolones remain the most effective preventive measure for neutropenic sepsis. A topic expert noted that even with the safety issues highlighted in the DSU, the benefits of fluoroquinolones in terms of reduction in potentially life-threatening infections outweigh the risks.

Although the DSU has highlighted rare but serious side effects of fluoroquinolones, the restrictions announced by the DSU are aimed at treatment of mild to moderate infections, whereas fluoroquinolone use in the neutropenic sepsis guideline relates to prevention of potentially fatal infections (though the DSU does not specifically discuss prophylaxis of serious infections).

After considering the evidence originally examined by the guideline, the content of the DSU, new evidence identified since the guideline was published, and the limited response from topic experts (a haematological oncology specialist), we judged that the conclusion of the original guideline committee – that the benefits of fluoroquinolones in saving lives outweigh potential harms – remains valid.

There is therefore no impact of the DSU on recommendation 1.2.1.1 to offer prophylaxis with a fluoroquinolone, but a link to the DSU will be added to the recommendation. A footnote will also be added to explain that fluoroquinolone antibiotics currently available in the UK are not licensed for prophylaxis of neutropenic sepsis and the recommendation is for off-label use.

Exceptional surveillance summary

The NICE guideline on neutropenic sepsis covers preventing, identifying and managing neutropenic sepsis in children, young people and adults receiving treatment for cancer in the community and in secondary and tertiary care.

The guideline currently recommends offering prophylaxis with a fluoroquinolone during the expected period of neutropenia only for adults (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count 0.5×10^9 per litre or lower) is an anticipated consequence of chemotherapy.

In March 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) published a Drug Safety Update (DSU) with restrictions and precautions for the use of fluoroquinolone antibiotics because of rare reports of disabling and potentially long-lasting or irreversible side effects.

The DSU lists conditions for which fluoroquinolones should not now be prescribed including non-severe or self-limiting infections, or non-bacterial conditions, and for some mild to moderate infections unless other antibiotics are considered inappropriate. General precautions are also noted for prescribing fluoroquinolones, including for patients at increased risk (age over 60 years, renal impairment, receipt of solid-organ transplantation, or treatment with a corticosteroid being risk factors for tendon damage).

However, the DSU additionally notes that restrictions should not prevent use of a fluoroquinolone for serious or severe infections if this is consistent with UK national guidance or where there are microbiological grounds, and where the benefit is thought to outweigh the risk. Fluoroquinolone prophylaxis of neutropenic sepsis is not specifically discussed.

We added an alert about the DSU to the landing page of the neutropenic sepsis guideline to advise readers immediately about this safety concern.

NICE's multidisciplinary standing committee for antimicrobial prescribing guidance were then asked to consider the impact of the DSU on all NICE guidelines that currently recommend fluoroquinolones, including the neutropenic sepsis guideline. The committee discussed some possible changes to the guideline, but their lack of expertise in oncology

or haematology led them to conclude that an exceptional surveillance review of the guideline should be undertaken, to allow engagement with topic-specific experts, to decide whether to update the recommendations relating to fluoroquinolones.

Methods

We considered evidence on effectiveness and safety of fluoroquinolones and other agents for prophylaxis of neutropenic sepsis by checking:

- the evidence considered when developing the guideline in 2012
- the evidence considered in the 2019 routine surveillance review of the guideline
- new or updated Cochrane reviews.

We also considered:

- topic experts' views on fluoroquinolone prophylaxis of neutropenic sepsis
- whether any new information had equalities implications.

We decided that full updated literature searches were not needed because the information we had from the original guideline, routine surveillance, Cochrane reviews and topic experts, was enough to establish whether an update to the guideline was needed.

Information considered in 2012 when developing the guideline

When developing the guideline (see NICE's full guideline on neutropenic sepsis), the guideline committee assessed the clinical and cost effectiveness of prophylactic treatment with antibiotics, growth factors and granulocyte infusion.

Clinical evidence

Among 202 randomised controlled trials examining primary prophylaxis, the evidence showed that prophylactic fluoroquinolones were more effective than placebo at reducing overall short-term mortality (for example, death within 30 days of fever onset) and reducing febrile neutropenia. The relative effectiveness of prophylaxis with

fluoroquinolones compared with co-trimoxazole at reducing short-term mortality was uncertain. Evidence for the effectiveness of fluoroquinolones compared with co-trimoxazole in preventing febrile neutropenia was mixed.

Compared with no prophylaxis, antibiotic prophylaxis increased the likelihood of infection with bacteria resistant to the antibiotic used for prophylaxis, though the effect of fluoroquinolone compared with no prophylaxis on infection with bacteria resistant to quinolones was uncertain. Colonisation with bacteria resistant to fluoroquinolones was more likely in patients who had received fluoroquinolone prophylaxis than no prophylaxis, but co-trimoxazole was more likely than a fluoroquinolone to lead to infection or colonisation with bacteria resistant to the antibiotic used for prophylaxis.

The guideline also considered evidence on prophylactic colony stimulating factors (CSFs), which showed that they did not reduce overall short-term mortality compared with placebo, but did reduce febrile neutropenia.

Cost-effectiveness evidence

A de novo economic model was built for the original guideline comparing primary and secondary prophylaxis with placebo, quinolones, granulocyte (macrophage) CSF (G[M]-CSF), G(M)-CSF plus quinolones, or pegylated granulocyte CSF (PEG-G-CSF).

The model showed that in solid tumours, primary prophylaxis with fluoroquinolones was more cost effective than other strategies, which was robust to sensitivity analysis. G(M)-CSF and G(M)-CSF plus fluoroquinolone reduced neutropenic sepsis in some populations but the incremental cost-effectiveness ratio was far above £20,000 per quality-adjusted life year. For patients with solid tumours who cannot receive fluoroquinolones, no prophylaxis was shown to be most cost effective but was sensitive to adjustments in the model, so no recommendations were made. PEG-G-CSF was also cost effective in these patients, but only after substantial price discounts.

Conclusions

Clinical evidence showed that prophylactic fluoroquinolones were more effective than placebo at reducing mortality and neutropenic sepsis. Health economic modelling found that primary prophylaxis with fluoroquinolones in solid tumours was more cost effective than other strategies. Based on clinical experience, the committee felt that other patient groups (namely those undergoing stem cell transplantation, or intensive treatment for

acute leukaemia) would also benefit from antibiotic prophylaxis and the additional costs would be small and vastly outweighed by the improvement in short-term mortality. The substantial cost of colony stimulating factors put them far above NICE's standard cost-effectiveness thresholds.

The committee noted benefits of fluoroquinolones would be fewer deaths and hospital admissions and potentially improved quality of life. They noted risks, such as resistant bacterial infections and super-infection with *Clostridium difficile*, and that monitoring for antimicrobial resistance should be carefully undertaken. However, based on clinical experience, they noted that deaths from infections in this population are likely to be less than deaths from neutropenic sepsis. They also noted potential side effects of fluoroquinolones but agreed that the benefit of saving lives outweighed potential harms.

On this basis, the guideline committee decided to recommend offering primary prophylaxis with a fluoroquinolone during the expected period of neutropenia only in patients aged 18 years and older with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia is an anticipated consequence of chemotherapy.

It should be noted that fluoroquinolone antibiotics currently available in the UK are not licensed for prophylaxis of neutropenic sepsis and the recommendation is for off-label use.

Information considered in routine surveillance of this guideline

A routine surveillance review in 2019 checked whether the neutropenic sepsis guideline should be updated. The decision was published in February 2019, before publication of the DSU in March 2019. The surveillance review followed the static list review process, therefore only new or updated Cochrane reviews were searched for. Seven of the reviews identified assessed prophylaxis.

One review of antibiotic prophylaxis found no significant difference between quinolone and co-trimoxazole prophylaxis for death from all causes or infection, but quinolones were associated with significantly fewer side effects leading to discontinuation and less resistance to the drugs. The authors of this review concluded that among all antibiotics examined, the most significant reduction in mortality was with quinolones. The evidence supported the current recommendation to offer fluoroquinolones for prophylaxis of neutropenic sepsis.

The other 6 reviews on prophylaxis assessed colony stimulating factors or granulocyte transfusions. The evidence was either low quality, unclear or insufficient, and did not impact current recommendations to not routinely offer granulocyte CSF (G-CSF).

Topic expert feedback gathered for the surveillance review did not include any comments on fluoroquinolones or prophylaxis generally. Overall, the surveillance review concluded that there was no new evidence to justify an update of the guideline.

During consultation on the surveillance decision, no issues were raised about pharmacological prophylaxis, though a stakeholder noted that the guideline does not offer advice on patient isolation and appropriate treating environment. The final surveillance report stated that this may be considered in future updates to the guideline.

Additional information considered in this 2020 exceptional surveillance review to assess the role of fluoroquinolones

In March 2019, the MHRA published a DSU on fluoroquinolone antibiotics, announcing restrictions and precautions for the use of fluoroquinolone antibiotics because of rare reports of disabling and potentially long-lasting or irreversible side effects. The aim of the current exceptional surveillance review was to consider any impact of the additional safety issues set out in the DSU on the interpretation of the evidence by the original guideline committee that the benefits of fluoroquinolone prophylaxis outweigh the risks.

We also considered:

- new or updated Cochrane reviews published since the previous surveillance review
- topic expert feedback.

Clinical effectiveness of fluoroquinolones

A Cochrane review identified by the 2019 routine surveillance of the guideline concluded that among all antibiotics, the most significant reduction in mortality was with quinolone prophylaxis. Quinolones were also associated with significantly fewer side effects leading to discontinuation and less resistance to the drugs than co-trimoxazole. No further Cochrane reviews of antibiotic prophylaxis were identified by the current exceptional

review.

The clinical evidence base is consistent with the current recommendation to offer fluoroquinolone prophylaxis.

Clinical effectiveness of colony stimulating factors

The 2019 routine surveillance of the guideline found 6 Cochrane reviews of granulocyte transfusions or colony stimulating factors, but the evidence was low quality, unclear or insufficient. No further Cochrane reviews of granulocyte transfusions or colony stimulating factors were identified by the current exceptional review.

The clinical evidence base is consistent with the current recommendation to not routinely offer G-CSF prophylaxis.

Topic expert feedback

We contacted 12 topic experts (consultant oncologists and haematologists) who were recruited to the NICE Centre for Guidelines panel of Expert Advisers. They were sent a summary of the considerations of the guideline committee when originally making the recommendations. We asked the experts if the recommendation to offer fluoroquinolone prophylaxis was still valid given the safety alert, and if they would still use fluoroquinolones as a first-line option for prevention of neutropenic sepsis. Reminders were sent to experts who did not respond to the initial message.

We received feedback from 1 topic expert in haematological oncology who stated that despite the safety alert for fluoroquinolones, the benefits in terms of reduction in potentially life-threatening infections outweigh the additional risks. The expert also thought that the incidence of serious adverse reactions to fluoroquinolones was likely to be low relative to the frequency of neutropenic sepsis in patients with prolonged neutropenia, and that the recommendations are still valid. However, they also drew attention to the additional cautions in the DSU, specifically to discontinue fluoroquinolones at the first sign of tendonitis, and to prescribe with special caution in patients at increased risk (age over 60 years, renal impairment, receipt of solid-organ transplantation, or treatment with a corticosteroid).

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We concluded that new evidence on fluoroquinolones indicates that they are effective for prophylaxis of neutropenic sepsis. Neutropenic sepsis can be fatal, and fluoroquinolones remain the most clinically and cost-effective preventive measure. Although the DSU has highlighted rare but serious side effects of fluoroquinolones, the restrictions announced by the DSU are aimed at treatment of mild to moderate infections rather than prevention of potentially fatal infections.

After considering the evidence originally examined by the guideline, the content of the DSU, new evidence identified since the guideline was published, and the limited response from topic experts, we judged that the conclusion of the original guideline committee – that the benefits of fluoroquinolones in saving lives outweigh potential harms – remains valid.

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