Title

Empiric versus pre-emptive antifungal strategy in high-risk neutropenic patients on fluconazole prophylaxis: a randomized trial of the European Organization for Research and Treatment of Cancer (EORTC 65091)

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Plain word title:

Fever-driven versus test-driven antifungal treatment in patients with leukaemia who are on chemotherapy and antifungal prevention

Glossary

- *Antifungal drug* – medication used to prevent or treat serious fungal infections
- *Beta-D-glucan (BDG)* – a substance made by fungi that can be detected in the blood in patients with serious fungal infections
- *Empirical treatment* – treatment based on best-guess or suspicion rather than on a definitive diagnosis
- *European Organization for Research and Treatment of Cancer (EORTC)* – A non-profit clinical cancer research organization based throughout Europe
- *Galactomannan* – another substance made by different fungi that can be detected in the blood in patients with serious fungal infections
- *Invasive Aspergillosis* – when the mould called Aspergillus gets into the lungs and causes a serious infection. Aspergillus is all around us, but only infects people with a very low immune system.
- *Invasive Candidiasis* – when the fungus called Candida (which can cause thrush) gets into the blood stream and other organs and causes a serious infection. This can usually only happen in people who are already very unwell.
- *Invasive fungal infection* – a more general term for life-threatening fungal infections, which includes invasive candidiasis
- *Leukaemia* – a cancer of the blood and bone marrow
- *Prophylaxis* – medication given to prevent illness before it occurs

Summary of trial and results:

People being treated for leukaemia with strong chemotherapy may get life-threatening fungal infections, but they are very difficult to diagnose. Historically anti-fungal treatment is given for these infections based on clinical suspicion, this is called empirical or empiric treatment. Patients are usually given empirical treatment if they have an extremely weakened immune system from chemotherapy, and they have a fever that has not got better on antibiotics that treat bacterial infections. Most people who get antifungal treatment based on clinical suspicion do not have a fungal infection. People who get treatment for a fungal infection that they do not have could get all the side effects without any benefit.

The use of blood tests and CT scans to try and diagnose life-threatening fungal infections has been increasing recently. This means that treatment can be more targeted to those more likely to have infections, but with the risk that some people with fungal infections might be missed and not receive treatment.

In this study an experienced team of researchers in this area of clinical practice compared two approaches. The patients were adults being treated for acute leukaemia with chemotherapy or bone-marrow transplant. They received either:

- Standard 'empirical' fever driven plan - people with unexplained fever on anti-bacterial drugs (antibiotics) got anti-fungal drugs if they were not better after 4 days, or developed a new fever within 2 days.
- Test-driven 'diagnostic' plan - where people got regular blood tests for markers of fungal infection (galactomannan). If they had a diagnostic test positive for fungal infection, they got treatment with an anti-fungal drug, even if they did not have symptoms. Positive tests included; when the blood test was positive for galactomannan, signs of fungal infection on a chest scan, or if certain fungi were grown from the patient's sputum (phlegm).

In both approaches' patients got anti-fungal preventative treatment with fluconazole. If patients were started on anti-fungal drugs they had further investigations to try to prove or disprove the diagnosis.

This trial found that there was much less use of anti-fungal treatment in the diagnostic (regular galactomannan blood test) approach compared to the empirical fever-driven approach. There was no difference found in the number of severe fungal infections, nor in the number of people surviving to 42 and 84 days, between each approach.

Comment relating to the BioDriveAFS trial:

This trial is very important in relation to BiodriveAFS because the general approach is very similar. The researchers were comparing a regular blood test strategy to an empirical treatment strategy. BiodriveAFS will compare a regular blood test strategy

to an empirical strategy, however BioDriveAFS will use a galactomannan blood test as well as a second blood test called beta-D-glucan.

In this trial both patient groups got Fluconazole to try to prevent fungal infections. This is called prophylaxis (a preventative). However, Fluconazole does not have any effect on 'moulds' (a type of fungi) which cause the most common severe fungal infection in acute leukaemia, called Invasive Aspergillosis. Fluconazole mainly prevents Invasive Candida infections which are less common. In BioDriveAFS the empirical group gets an anti-mould drug that may prevent both types of infections, but the diagnostic group does not receive any preventative antifungal drug.

In this trial, a blood test (galactomannan) was used, which only detects Aspergillus for which these patients received no preventative (prophylactic) drug. In BioDriveAFS, the second blood test (beta-D-glucan) can also detect Candida and other fungal infections, including Invasive Aspergillosis.

Therefore, BioDriveAFS is using a very similar approach to this trial. This trial showed that a diagnostic driven strategy safely and considerably reduces antifungal use. BioDriveAFS is asking the next question, whether we can safely replace antifungal prophylaxis with regular blood tests as well. The results of the two trials together should identify the optimal approach used to prevent and manage fungal infections in acute leukaemia patients.