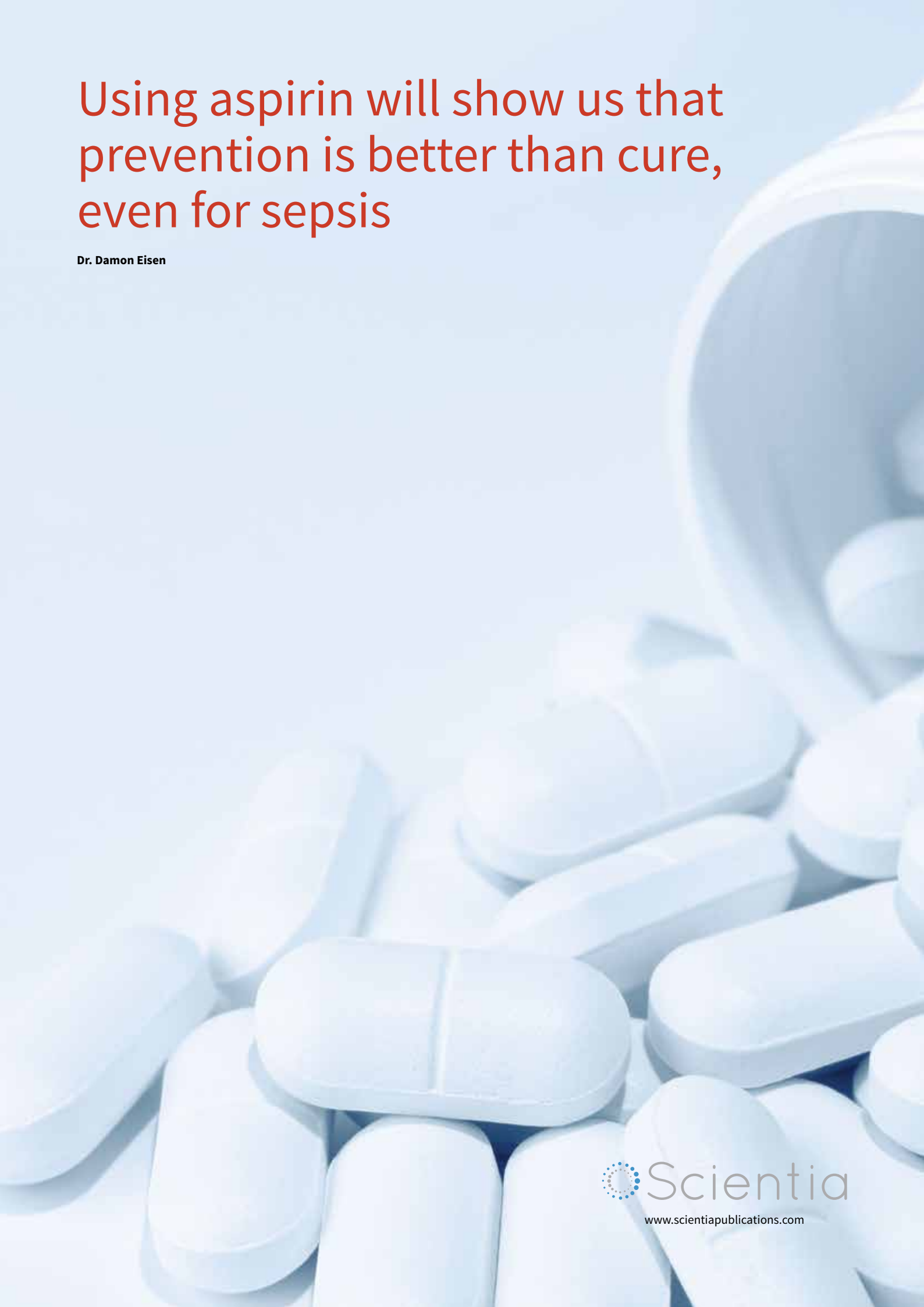
Using aspirin will show us that prevention is better than cure, even for sepsis

Dr. Damon Eisen



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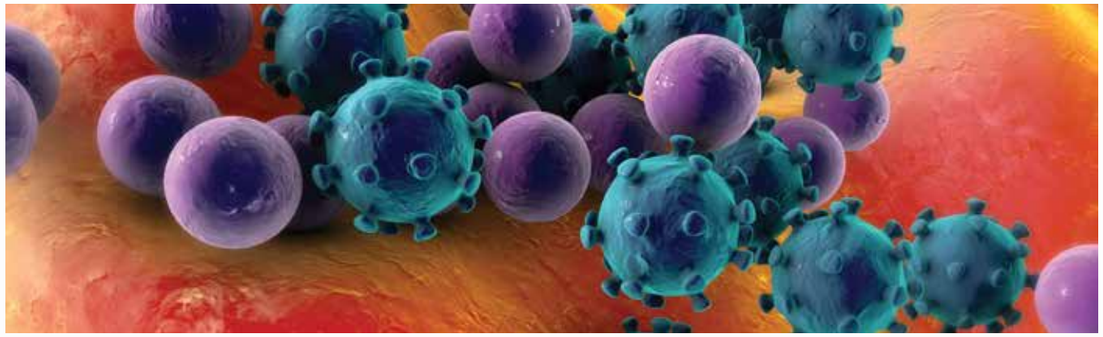
Dr. Damon Eisen has had a long career studying infectious diseases and their subsequent treatment. Here he discusses the use of aspirin as a preventative measure against the life-threatening condition known as sepsis.



To start with, could you explain how your research background led to your current interest in sepsis?

As an Infectious Diseases clinician researcher one learns to question ways in which common conditions are treated. This in turn prompts one to think if serious infections could be managed better. This certainly applies to sepsis.

Early recognition and treatment improves the outcome in sepsis. Antibiotics, intravenous fluids and other supportive therapies have greatly improved the survival in severe sepsis, but a stubborn 20-30 per cent of cases don't respond. It is these patients who need more treatments, ones that target the body's response to severe infection, to survive this incredibly common problem.

Where does your research fit in the larger context of current biomedical research?

The so-called 'adjuvant' treatments for sepsis trialled to date have all been used when the reaction to severe infection has commenced. An alternative approach is to prevent the consequences of severe infection.

Low-dose aspirin is an important candidate treatment, working not to prevent infection but by reducing the scale and intensity of the immune response. Aspirin can inhibit well-characterised biochemical pathways that mediate sepsis. Doses as low as 81 mg a day can prevent further development of sepsis-related inflammation, as well as ameliorating established sepsis. These factors may be the key to effective use of aspirin to prevent sepsis. It can be taken daily, safely and cheaply, and it may dampen the life threatening immune response sepsis.

What have you discovered so far from the aspirin/sepsis trials?

Our main results will derive from the ANTISEPSIS study, a ground-breaking, world-first trial using a population of patients in a randomised controlled trial, where we will be able to analyse the association between aspirin usage and mortality from sepsis in participants aged over seventy.

We have completed a large observational cohort study of patients with systemic inflammatory response (SIRS), many of whom had proven sepsis. A total of 7945 ICU admissions to St Vincent's Hospital, Melbourne, between April 2000 and November 2009 were examined. The probability of in-hospital death for individuals who were identified as having SIRS or sepsis was analysed according to whether they were on aspirin prior to their admission. Among the 5523 elderly patients with a first episode of SIRS, 2082 were administered aspirin in a 24-hour period around the time of SIRS recognition. Propensity analysis showed reduced numbers of deaths with 10.9 per cent mortality for aspirin users and 17.2 per cent mortality in non-users. There were potential side effects though as aspirin administration was associated with increased risk of renal injury (6.2 per cent versus 2.9 per cent). In the 970 patients with proven sepsis, aspirin administration was associated with a lower mortality (27.4 per cent vs. 42.2 per cent). This observational study provides vital preliminary data to make us examine this important issue prospectively.

How do you envision aspirin-based treatments will be implemented?

If low dose aspirin is shown to be effective and safe in preventing death due to sepsis it would be quickly adopted for that indication and it would be incorporated into the preventive medicine strategy for adults at risk of severe infection.

What long-term consequences might this study have on future work and potentially on healthcare, society and policy?

Results from our large observational study of critically ill patients indicated the number needed to treat with low dose aspirin to prevent death due to SIRS or sepsis was between seven and 16. If these data are indicative of the benefit found in the ANTISEPSIS study, then the use of low dose aspirin would be enormously cost-effective. Even if lower reductions in mortality are shown then this along with evidence that low-dose aspirin affects sepsis-related outcomes in the elderly in terms of hospitalisation, ICU admission, and death would be a new and significant scientific advance.

Poisoned blood and willow trees

James Cook University is the second-oldest in Queensland, Australia. They are well known for their pioneering work on both tropical infectious diseases and marine biology.

We sometimes forget in this age of advanced medicine, of transplanted organs and genetic therapies, that many truly classic medicines still hold their own. One of these, steeped in history, is aspirin, a compound found almost ubiquitously in medicine cabinets around the world. Its origins lie in treatments made from willow-tree bark, known since ancient Greek times to be effective against pain and fever, and stretch to the discovery in the 1800s of acetylsalicylic acid. Acetylsalicylic acid, better known by the brand name Aspirin, is converted within the body to the active ingredient in willow bark, itself known as salicylic acid.

The long history of aspirin has led to a number of studies into the impressively wide range of diseases it can treat. This naturally includes pain, fever, and inflammation, but also the prevention of heart attacks, strokes and blood clots – indeed aspirin is often given after heart attacks to reduce the likelihood of another attack. Further support for aspirin's broad efficacy comes from clinical researchers such as Dr. Damon Eisen, who has spent several years examining its effect on one of medicines long-known foes: sepsis.

The Egyptians wrote about Sepsis, it was commented on by Hippocrates yet it's still a scourge of modern medicine. But what is it? It begins with an infection, in the lungs, the urinary tract, the brain, etc. This sets off an inflammatory response in the body, essentially a far larger version of the swollen redness seen around infected wounds. Internally, inflammatory signalling proteins are circulating throughout the body, inducing this response wherever they go. Within the bloodstream, platelets begin to activate, thickening the blood and leading to hypertension and clotting. Lymphocytes and neutrophils, two types of white blood cell, begin to commit cellular suicide, harming both the protective immune response and extending the inflammatory process. The combination of these effects can lead to organ failure and death. Despite numerous studies focusing on this age-old disease, it remains deadly: approximately one third of patients with severe sepsis will die, killing over 200,000 each in year in the USA alone.

Why is sepsis so deadly? In part this is due to the speed at which it progresses, often too fast for doctors to adequately react. As such the ideal treatment would be a preventative one, helping to support the body prior to disease onset. As such, much attention has been focused on the expected results of a trial known as ASPREE. ASPREE, short for Aspirin to Prevent Events in the Elderly, is a preventative trial, essentially asking whether daily low doses of aspirin can reduce the risk of elderly patients developing heart problems or dementia, amongst others. This trial is running in both Australia and the US, and will follow 19,000 patients over the course of 5 years.

Aspirin is able to treat a wide range of diseases, should sepsis be added to the list?

A subset of this trial is known as ANTISEPSIS, an acronym derived with some flexibility from AspiriN To Inhibit SEPSIS. This sub-trial will use patient questionnaires alongside hospital records to determine whether this low-dose aspirin treatment acts to prevent sepsis. Dr. Damon Eisen, head of this sub-study, is confident that it will, as he has previously conducted smaller observational studies in the field. One of these studies, examining almost 8000 hospital admissions, indicated that patients who had been given aspirin in the 24 hours surrounding the diagnosis of sepsis had a significantly lower chance of dying – 10.9% vs 17.2%. Given the number who die of sepsis each year, reduction could lead to thousands of lives saved.

How is aspirin able to achieve this? Aspirin is a member of the non-steroidal anti-inflammatory drugs, (NSAIDs for short), other members of which include ibuprofen and naproxen. It acts by targeting and modifying enzymes known as cyclooxygenases, which produce a number of signalling molecules and hormones to control various aspects of physiology. Once aspirin has altered cyclooxygenase-2 the enzyme increases production of the molecule known, simply enough, as 15R-hydroxyeicosatetraenoic acid. This then passes through a complex chain of enzymes, cell types, and signalling processes, with the end effect of reducing inflammatory signals and encouraging the clean-up of dead cells. In doing this it reduces the length and severity of sepsis attacks, allowing doctors time to support the patient and bring them through with better chances.

If the ANTISEPSIS trial shows the expected benefits from aspirin treatment, it will have a major effect on current sepsis treatment plans. Aspirin is both cheap (as Dr. Eisen comments, "use of low dose aspirin would be enormously cost-effective") and has a long history of safe use, as such it would be readily integrated into preventative regimens. Time will tell if Aspirin will have yet another chapter added to its long and storied history.

Researcher Profile

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After completing his Bachelor of Medicine/Surgery, Dr. Eisen focused his talents on the blood-borne parasite Plasmodium falciparum, research that led to a Doctorate of Medicine from the world-class University of Melbourne. This focus on infectious disease led to studies on the effect of aspirin on S. aureus infections, and in turn to work on the ASPREE study. Dr Eisen has had a fruitful career, having his name on 80 publications, including three in the Lancet and one in Nature Medicine, and undoubtedly many more to come.

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