

Penicillin: The Old/New Wonder Drug

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Abstract

Penicillin (PCN) has been shown to treat psoriasis effectively and be curative in many cases. Streptococcus is the organism responsible for beginning the process and has previously escaped detection by moving intracellularly or by forming biofilms. The treatment is low dose for many months and thus is similar to rheumatic fever. Arthritis has been shown to be caused by biofilm-forming dental and Lyme spirochetes, and these organisms, like the streptococcus in psoriasis, have escaped detection. Penicillin, plus a biofilm-dispersing agent is effective in treating arthritis in which tissue destruction has not already occurred.

Alzheimer's disease has been shown to be caused by those same spirochetes involved in arthritis, and, in every way, similar to the dementia of neurosyphilis caused by *Treponema pallidum*. These organisms make biofilms that induce B amyloid and a Toll-like receptor 2 response leading to tissue destruction. Penicillin given prior to the organisms arrival in the brain (or before they create biofilms) would effectively prevent dementia in Alzheimer's as it does in syphilis. We have shown that biofilm-forming staphylococci are integral to the etiology of atopic dermatitis. Along with standard corticosteroid therapy, antibacterial treatment, as opposed to antibiotics, appears to be a better treatment in AD because all the organisms are multi-drug resistant and 60% are MRSA or MSRE. Treatment with PCN in psoriasis, arthritis, and syphilis, has thus far not led to resistance and may actually prevent resistance by killing organisms before they make biofilms and share resistance genes.

Keywords: Penicillin; Streptococcus; Alzheimer's disease; Antibiotics

Introduction

From its very first use in the USA in 1942, where it completely reversed a downward spiralling case of streptococcal puerperal fever, penicillin has claimed status as a "miracle" drug. After treatment and convalescence, this most fortunate patient lived another 57 years and died in 1999, at the advanced age of 90.

Although it was discovered in 1928 by Alexander Fleming, a microbiologist at St. Mary's Hospital in London, penicillin languished for more than a decade before its importance was noticed. As its antimicrobial properties became more apparent, large enough quantities were produced for clinical trials through the efforts of Florey et al. [1]. Then came World War II, and the U.S. government became intensely interested in penicillin because, in previous wars, soldiers were more likely to die from wound infections than from the wounds themselves. The government was anxious for anything that would reduce American casualties, and it made penicillin production a priority. More than 20 companies were encouraged to join the effort to produce sufficient quantities of penicillin for the military. Production ramped up so much that by the invasion of Normandy in June 1944, companies were producing 100 billion units of penicillin per month.

Since then, the penicillin have been used in a wide spectrum of diseases caused by Beta hemolytic *Streptococcus pyogenes* (including streptococcal pharyngitis, rheumatic fever and scarlet fever amongst many others), *Diplococcus pneumoniae*, *Neisseria gonorrhoea* and meningitidis, syphilis and gonorrhoea [2]. The antibiotic, which contains a β -lactam group, is now known to wield its antibiotic power by preventing the formation of peptidoglycan cross-links in the bacterial cell wall. A number of semisynthetic penicillin derivatives improving on the properties of penicillin have been developed since penicillin was first commercialized. Ampicillin, patented by Beecham in 1961, improved the oral absorption of penicillin. Amoxicillin, also patented by Beecham in 1964, further improved oral absorption. These compounds and other penicillin derivatives share the β -lactam nucleus but have different side chains.

Penicillin's efficacy toward various microbes, its wide distribution in the human body, and its low systemic toxicity has given it a significant impact in the field of infectious disease. Although resistance to penicillin has emerged, it remains a very common antimicrobial treatment [2]. In addition to its current uses, this article will explore other potential indications for penicillin, some of which have already been discussed more than 5 decades ago. Further, because of the recent recognition that microbes may form biofilms or internalize within cell cytoplasm, and thus not be available to either the immune system or antimicrobial antibiotics, the impact of antibiotics, as currently utilized, has been drastically diminished.

Old Applications

Syphilis

For centuries, syphilis stood as one of the most devastating diseases facing society. Sir William Osler's adage "he who knows syphilis, knows medicine" finds its veracity in the recognition that syphilis has the potential to cause pathology in most organ systems. Patients faced with the severe complications of tertiary syphilis were initially vainly treated with permutations of mercury and arsenicals. Prior to the advent of penicillin, it is estimated that the incidence of primary and secondary syphilis was 66.4 cases per 100,000 in the United States [3]. The introduction of penicillin in 1943 led to a rapid decline of 3.9 cases per

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100,000 by 1956 [3]. The publication on the treatment of four syphilitic patients with penicillin by Mahoney et al was soon quickly followed by a case report of the successful resolution of tertiary cutaneous syphilis with penicillin [4]. While the earliest trials of penicillin often failed in hindsight due to incorrect dosing or impurities, the burgeoning success of penicillin in treating tertiary syphilis originally with 320,000 U of penicillin over an 8 day time period lent credence that the cure to syphilis would lay in the newfound drug [5]. Old treatments quickly died out and penicillin abruptly became the mainstay.

Even today, penicillin continues to be the gold standard of therapy for syphilis. The dosage and duration of treatment vary per stage, with oral penicillin often not achieving adequate blood levels. First line therapy for early syphilis remains benzathine penicillin. Probenecid has also been used to amplify drug levels in the serum and CSF [3]. Late latent stages of syphilis have been difficult to ascertain proper levels and dosing of penicillin with the current accepted recommendations being a three dose regimen [6]. Cardiovascular syphilis necessitates three doses of benzathine penicillin, 2.4 mU, at weekly intervals [7]. Neurosyphilis, as one of the most devastating sequelae to syphilis infection, relies strongest on the prevention of further damage and/or progression to tabes dorsalis and general paresis. While the damage caused cannot be reversed, a high resolution rate is found with crystalline penicillin G, 12-24 mU daily for 10 to 14 days or procaine penicillin 2.4 mU daily with probenecid, 500 mg p.o. four times a day, both for 10 to 14 days. Benzathine penicillin cannot achieve adequate levels within the CSF [3]. Tertiary syphilis has been virtually eliminated by treatment of earlier stages of syphilis; this has been immensely aided by a serologic test that is exceedingly sensitive. However, the fact remains that treatment early in the course of this spirochetosis has prevented tertiary syphilis from occurring.

Streptococcal infections

The most common use for penicillin in the present day is for the treatment of streptococcal infections. *Streptococcal pneumoniae* continues to pose a lethal disease course even in the post-vaccination era, presenting in the pediatric population particularly in the form of otitis media or in the general population as pneumonia and meningitis. Despite resistance rates, *S. pneumoniae* continues to have an adequate response to penicillin, particularly in the situations of pneumonia or meningitis. Guidelines continue to dictate that patients with or at risk for splenic dysfunction such as sickle cell anaemia are suggested to begin penicillin prophylaxis in children upon diagnosis or at least by two months of age [8]. The PROPS study determined dosing with sickle cell disease children younger than five recommended to take penicillin V potassium 125 mg twice daily, and children over five penicillin V potassium 250 mg twice daily [9]. Prophylaxis with penicillin may generally be discontinued upon five years of age unless the patient has suffered a previous severe pneumococcal infection or has functional asplenia [8].

Mild soft tissue, middle ear, and skin infections along with pharyngitis are the acute illnesses associated with group A streptococcal infection with delayed complications being scarlet fever, rheumatic fever, post-streptococcal glomerulonephritis, and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). While it is still uncertain whether penicillin may impact glomerulonephritis or PANDAS once pathology has already set in, treatment is critical for cessation of primary disease progression and prevention of rheumatic fever, which will be discussed later [10]. Scarlet fever is one of the most diagnostic cutaneous presentations of GAS infections with the distinctive papular erythematous "sandpaper"

rash [11]. The cutaneous manifestation typically accompanies the pharyngeal infection with the rash emerging due to erythrogenic toxins produced by the bacterium [10]. Treatment remains a ten-day course of oral penicillin VK or erythromycin, or a single intramuscular injection of penicillin G benzathine. If administered within 1 week of onset of acute pharyngitis, acute renal failure may be prevented [12].

Rheumatic fever

Likewise, penicillin has equally revolutionized the treatment of rheumatic fever and the subsequent cardiac complications. Acute rheumatic fever occurs 2-3 weeks following infection of the pharynx by Group A streptococcus (GAS) [13]. Manifestations of acute rheumatic fever include arthritis, chorea, erythema marginatum and most importantly, carditis. Reinfection by GAS notably leads to valvular destruction and eventual heart failure [14]. While the reason exactly why infection by GAS causes rheumatic fever has yet to be determined, current hypotheses stipulate a relationship between the M protein of the bacterium, biofilm formation, and molecular mimicry between antibodies against bacterial proteins and cardiac membranes. Work by Catanzaro et al. noted that the development of rheumatic fever required living streptococci throughout the convalescent period, making penicillin treatment and prophylaxis essential [15].

Treatment of acute rheumatic fever involves penicillin in alternate roles. Prevention of acute rheumatic fever is essential and relies on quick diagnosis and treatment of streptococcus infection with penicillin or penicillin derivatives. The advent of penicillin and rapid antibiotic treatment of streptococcus has greatly contributed to the decline of rheumatic fever in the developed world. For patients with acute rheumatic fever, therapy relies on secondary prevention. Benzathine penicillin G administered intramuscularly over 4 weeks is the preferred choice. Continued administration of penicillin for prolonged periods of time, depending on age of infection, is warranted. Generally a minimum of five to ten years of prophylaxis is recommended, significant valvular damage necessitates lifelong prophylaxis [16]. Penicillin is ideally provided intramuscularly as oral prophylaxis falls prey to patient adherence and even with optimal adherence has a higher risk of recurrence [17]. As in syphilis, early administration of penicillin has led to near disappearance of rheumatic fever (except for occasional outbreaks) [18].

New Applications

While penicillin has made a significant impact on the above diseases, multiple studies have begun to shed light on the potential use of penicillin in other diseases. These include psoriasis, Lyme disease, multiple arthritides, and Alzheimer's disease, to name a few. Except for psoriasis, penicillin for these diseases is largely theoretical and conceptual, but the considerations for its usage are cogent. These considerations take into account the presence and impact of biofilm formation by the various organisms and the effect on the immune system (both innate and adaptive) that is generated.

Psoriasis

There are many lines of evidence leading to streptococcus as the antigen in psoriasis. The first is guttate psoriasis which has been shown to follow streptococcal pharyngitis. In plaque psoriasis, the "streptococcus as antigen" story is not as clear, and the reason is the organism can neither be cultured, nor does it generate any serologic evidence of its presence. This is due to internalization of the streptococcus into (tonsillar) cell cytoplasm and/or the production of biofilms [19]. Both of these phenomena lead to negative cultures and negative serologies.

There is recent immunologic evidence of streptococcus and plaque psoriasis: a streptococcal extract activates T-cells; and, further, there is a markedly elevated streptococcal specific IgG in the serum of plaque psoriasis patients represents humoral immunity [20]. Thus both arms of the adaptive immune system have been shown to be involved. The innate immune system has recently been shown to be involved also. Toll-like receptor 2 (TLR 2) has been found to be activated on the blood monocytes in psoriatic arthritis [21] and serum TLR 2 has been found in the upper dermal capillaries [22].

There is epidemiologic evidence as well: if there is no streptococcus in the environment, there is no psoriasis. Northernmost Europe and certain Pacific islands (including Australia among others) have demonstrated this [23]. If streptococcus is the antigen, then penicillin and other anti-streptococcal antibiotics should be beneficial. There is solid evidence for this, first from case reports and small series [24]; and second from 2 larger series, the first employing IM benzathine penicillin in which the results were spectacular (PASI 90-near total clearing) [25]. The second utilized oral azithromycin (with pulse dosing) again with remarkable improvement (PASI 75- marked clearing) [26]. These studies were conducted with the treatment rendered over a long period of time, which appears to be very important with this type of therapy, just as in rheumatic fever. The lengthy administration is likely necessary due to the aforementioned internalization of the organism or the presence of the biofilms. The penicillin would be present and bactericidal when the organism externalized or emerged from the biofilm. Moreover, the serum antibody needs to decay; this very likely also contributes to the prolongation of the treatment.

The administration of the penicillin may be similar to that of Saxena, with IM bicillin, or may be similar to rheumatic fever with 250 mg oral penicillin daily. The oral dose may be adjusted as well; and instead of a “pulse” of azithromycin 500 mg daily followed by 10 days off, administration of 500 mg on each weekend day seems more practicable and may lead to better compliance. If the patients are not cured, as a percentage was not, a biofilm disperser could be considered for co-administration. In that regard, psoriasis straddles the old and the new penicillin where it is effective alone in the “old” cures; and, where in the “new” cures, it requires an additional agent to “break through” biofilms to kill the streptococci hidden within (Table 1). These agents, considered from a dermatological point of view, work either topically or systemically. An example of the topical use would be silver sulfadiazine which is widely used in burns. The systemic use of various agents, especially rifampin, is postulated for co-administration with penicillin (and/or other antibiotics). One agent that is not listed in Table 1 that has emerged as an important biofilm disperser is L-serine. L-serine has

Topical	Systemic
Gold [30]	Niacinamide [31]
Silver [32-37]	Furans/Furan Precursors: [38-41]
Platinum [42]	- Nitrofurantoin
Selenium [43-45]	- Citalopram
Cinnamates [46-48]	- Pregabalin
Tannic acid [49,50]	Hydroxychloroquine [51,52]
Curcumin [53]	Rifampin [54,55]
Honey [56]	Ascorbic Acid [57,58]
Hyaluronidase [59]	Quinolones [60,61]
L-tryptophan [62]	Piperidines [63] (donepezil, haloperidol)
Flavanoids [64]	Pyroles [65] (resperidine, celecoxib)
Cysteine [66]	Thiophenes [67] (olanzapine)

Table 1: Biofilm dispersers and inhibitors.

a role in the prevention and treatment of Alzheimer’s disease, as will be mentioned below. The next diseases to be discussed all require such co-administration.

Surgery is another way to remove the streptococcus and tonsillectomy has been shown to have a beneficial effect [27,28]. There are other foci other than the tonsils where streptococcus can be found; there have been reports on perianal streptococcus and guttate psoriasis. However, cutaneous streptococcus has been more aligned with glomerulonephritis than to psoriasis [29]. Lyme disease, where Lyme spirochetes (Borrelia) have been found in the brains of Alzheimer’s disease, this makes Lyme disease similar to syphilis caused by the spirochete *T. pallidum*. In fact, it appears to follow a similar course with primary (*Erythema migrans*), secondary (generalized systemic symptoms), and tertiary (brain, heart, joints) stages [68,69]. Further, the pathology of syphilis has recently been shown to be the same as Alzheimer’s disease [70]. We have shown the plaques in Alzheimer’s disease represent biofilms [71]. These most assuredly are made by the organisms; in the instance of General Paresis, they would be made by *T. pallidum*, and in the case of AD, they would be caused by dental spirochetes (75%) and Lyme spirochetes (25%) [70]. All these organisms are sensitive to penicillin in their planktonic state; thus it seems most reasonable to treat them just like syphilis (before they arrive in the brain or before they do damage) [71].

In addition, syphilis that is untreated progresses to tertiary in only 35% of patients; it seems no coincidence that Lyme disease treated with doxycycline shows tertiary findings in 35% of the patients [72-74]. It is almost as if treating the disease with doxycycline may lead to resolution of erythema migrans, but otherwise is like no treatment at all.

Arthritides

Dental and Borrelia spirochetes have been associated with arthritis [75,76]. In turn, these organisms have both been shown to cause biofilms that lead to arthritis. In a recent work regarding arthritis, seemingly sterile joints were found to contain biofilm [77]. The microbes are relatively slow in causing symptoms and joint destruction and often take many years. Frequently, the disease they create is termed “wear and tear arthritis.” [77] In light of the other spirochetal biofilms and the destruction they are associated with, it is probable that the innate immune system is involved [78]. Where these organisms are generating biofilms, they are unrecoverable except by PCR. With rheumatoid arthritis, the destruction is much more severe and much more rapid [79]. This is likely due to the adaptive immune system being activated [80].

With this as background, a small pilot study was undertaken to see if penicillin and a biofilm disperser would ameliorate the arthritis. 7/10 patients taking this protocol showed relief of symptoms; the 3/10, who did not have symptom relief, needed joint replacement within 3 months [81]. These preliminary results indicate that penicillin given with a biofilm disperser is most beneficial for osteoarthritis. For rheumatoid arthritis, where the adaptive immune system is at work and it carries all the destructive capacity of immunoglobulins, complement, alternate pathway and T cells, it seems that early intervention with penicillin and a biofilm-dispersing agent would be most prudent. If the subsequent destruction were to be prevented by this approach, then penicillin would once again be included in the “wonder drug” category.

General Paresis of the Insane and Alzheimer’s Disease

General paresis of the insane (GPI) (tertiary syphilis) was the most common type of dementia through the first half of the twentieth century

[82]. It was first thought that GPI was caused by chronic inflammation in the arachnoid lining of the brain until Esmarch and Jessen in 1857 raised the hypothesis of causal relationship between syphilis and GPI. Once *T. pallidum* was discovered and once the efficacy of penicillin became evident, any treatment with penicillin prior to tertiary syphilis was curative. However, GPI patients treated with penicillin were not able to gain memories that were already lost. With this as background, it was proposed that early treatment and prevention with penicillin would be necessary to prevent the progression of the disease certainly prior to the cognitive and behavioral signs of GPI [82]. The efficacy of penicillin in treating GPI shaped the approach to controlling Alzheimer's disease, which was only recognized in 1960s to be the most frequent dementia, previously known as senile dementia, seen in elderly individuals [82]. Further reviews and studies confirmed that chronic infection with spirochetal infections can lead to dementia and produce the clinical and pathological hallmarks of AD with oral treponemes comprising 75% and Lyme treponemes 25% [70,83]. There have not been any studies on the treatment and control of AD using penicillin. However, in a recent historical review of the pathology of neurosyphilis, it was shown to be completely the same as Alzheimer's disease with plaques and tangles and severe neuronal loss [70].

Given the same pathology in Alzheimer's disease as syphilis and given similar spirochetal organisms sensitive to penicillin, treatment with penicillin before those spirochetes travel to the brain or before they create damage, would conceivably be curative just as it is in syphilis [71]. Succinctly, AD appears to be similar to syphilis except it is caused by a different spirochete. That similarity also extends to the primary, secondary, latent, and tertiary staging so familiar in syphilis. As in syphilis, treatment prior to tertiary is exceedingly important. Where it recently has been shown that the plaques in AD are formed by biofilms, the co-administration of a biofilm-dispersing agent along with the penicillin would be unlikely to reverse pathological changes, but may be able to help prevent further progression of the disease.

The importance of biofilms and biofilm-dispersing agents in the prevention of Alzheimer's disease, particularly L-serine, is eloquently illustrated in the observations of Cox et al. As an ethnobiologist, Dr. Cox was particularly fascinated with the markedly increased incidence of Lou Gehrig's, Parkinson's, and Alzheimer's diseases among the Chamorro people of Guam [84]. This was attributed to a unique diet high in beta-Methylamino-L-alanine (BMAA), a neurotoxic substance [84]. Meanwhile, distant Ogimi villagers on the Japanese island of Okinawa who ate a diet of tofu and seaweed that contained large quantities of L-serine did not have these diseases, nor did they have high rates of arthritis [82]. Dr. Cox's observations further corroborate the mechanism of action that we propose for the pathology and prevention of Alzheimer's disease: that a biofilm inducer, in this case BMAA activates the immune system and thereby causes tissue damage and disease; while a biofilm inhibitor via quorum-sensing inhibition, in this case L-serine does not induce an immune system activation, preventing tissue damage and disease.

In the diseases above, (psoriasis, Lyme disease, various arthritides and Alzheimer's disease), penicillin promises to be very effective, especially when co-administered with a biofilm "buster". All the organisms are capable of making biofilms and do so mostly through the "quorum sensing" mechanism they contain. The arthritides, linked epidemiologically to dental spirochetes, are the only diseases in the discussion where the penicillin sensitive microbes have not been identified in the tissue.

Conclusion

Few innovations have made the tremendous impact on the medical field as penicillin. Diseases today considered to be innocuous and quickly treated were once a death sentence for millions. Penicillin is well known throughout the medical community as the therapy for streptococcal infection, syphilis and acute rheumatic fever. Due to its efficacy and affordability, much effort needs to be put into investigation on the therapeutic role of penicillin in psoriasis, arthritides (including rheumatoid arthritis and osteoarthritis), Lyme disease and Alzheimer's disease. The association of streptococci and spirochetes with the corresponding diseases like psoriasis, Lyme disease, arthritides and Alzheimer's disease suggests treatment with penicillin can be just as miraculous as when it was first introduced.

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