The long road to PCP prophylaxis in AIDS. An early history.

September 23, 2009 By Joseph Sonnabend, MD

In my introductory post, I promised to write about some of my experiences in New York City at the very start of the epidemic, from both professional and personal perspectives.

This post is about preventing Pneumocystis pneumonia in AIDS.

It's a sad largely neglected history. Many lives were shortened before 1989 when interventions to prevent this type of pneumonia were finally recommended by government officials for people with AIDS.

Thankfully, with the widespread use of antiretroviral drugs, many people may not be too familiar with this opportunistic infection. It most certainly has not gone away, but in the 1980s Pneumocystis pneumonia was what most commonly killed people with AIDS.

It's now almost 30 years since the epidemic was first officially recognized in 1981. It was in the June 5th, 1981 edition of the Morbidity and Mortality Weekly Report (MMWR) published by The Centers for Disease Control (CDC), that the first cases of Pneumocystis carinii pneumonia (PCP) were first described. Click on this link to see an account of the first official report of AIDS, and the CDCs earliest responses.

In fact, this CDC report was *not* the first public mention of AIDS. The first time the as-yet unnamed disease was noted in the media was about three weeks earlier, on May 18th in the New York Native, a gay weekly newspaper in New York City. Larry Mass was the author of this report. As noted by Gabriel Rotello, it was the gay community in New York City that first brought the epidemic to public attention.

Many of us taking care of gay men in the late 1970s became aware that our patients were showing a number of unexplained signs and symptoms. I was one of these physicians and so I suppose I should have started these accounts of the early days at the beginning - at least, the beginning for me, as I became aware around 1979 that something very unusual was affecting so many of my patients, and realized that there was a developing problem with potentially immense implications. But I will leave this "pre-AIDS" account for another post.

In this post I address the preventable opportunistic infection, PCP that was the major cause of

death among people with AIDS in the first decade of the epidemic.

Because there are a number of immunological disorders that result in a susceptibility to similar opportunistic infections that are characteristic of AIDS, PCP had been well studied before AIDS appeared. When the epidemic began we knew how to diagnose this particular opportunistic infection, we knew how to treat it and we also knew how to prevent it.

As early as 1977 it had been well established that PCP could be prevented by an inexpensive medication, yet official recommendations for the use of this and other interventions as prophylactic agents against PCP in people with AIDS did not appear until 1989.

This long delay is a strange episode in the history of medicine, although it is barely remembered today. But anyone who experienced the first decade of the epidemic in the US will remember the scourge that was PCP.

Attempts to bring this effective prophylactic measure to attention had been made by individuals in the gay community well before its formal introduction in 1989, most notably by Michael Callen, an early AIDS activist who has since died.

First a few words about PCP. Thanks to antiretroviral medications this infection is now relatively uncommon. But it most certainly has not gone away. Although the name of the causative organism has been changed to Pneumocystis jiroveki from Pneumocystis carinii, we still recognize the pneumonia associated with it as PCP. The organisms interfere with the diffusion of oxygen into the blood, and untreated, the infection is almost always fatal, in effect causing death by suffocation.

To get an idea of the extent of the fatalities this pneumonia caused, Michael Callen asked a CDC statistician in 1989 how many AIDS related PCP deaths had occurred since the beginning of the epidemic. As of February 20th, 1989, 30,534 Americans had died of AIDS-associated PCP. The year is significant as it was then that the CDC finally issued recommendations for the prevention of PCP, using a drug that had been known to prevent this kind of pneumonia since 1977.

The drug in question is Bactrim, also known as Septra, Septrin or co-trimoxazole. It is actually a combination of two drugs, trimethoprim and sulfamethoxyzole. It has been available as an inexpensive generic product for many years.

Bactrim was first demonstrated to be an effective prophylactic agent against PCP in children with leukaemia by Walter Hughes in 1977. What about other immunocompromised conditions associated with a susceptibility to PCP? Dr. Hughes suggested in a 1981 publication that in these other immunocompromised conditions, where a first episode of PCP was known to be followed by a rate of recurrence of about 15%, Bactrim should be prescribed after the first episode.

In AIDS we soon learned that the rate of recurrence of PCP was about four times higher than the 15% threshold suggested by Walter Hughes as an indication for prophylaxis. By 1984, if not sooner, we knew that one episode of AIDS -related PCP was followed by another within a year in at least 60% of those initially affected. I don’t know if Walter Hughes made any proposals that PCP

prophylaxis in this new disease should be considered differently to his 1981 recommendations regarding the use of bactrim in immunocompromised conditions other than childhood leukaemia. He was a member of the CDC committee that recommended the use of Bactrim to prevent PCP in AIDS in 1989.

It is true that people with AIDS have a higher frequency of adverse reactions to Bactrim than those not infected with HIV. These are mostly hypersensitivity reactions including fever and rashes. But we soon learned that these reactions could be frequently avoided by a desensitizing process, involving a gradual increase in dose. We also learned that the initial dose proposed by Dr. Hughes in the 1970s and by the CDC committee in 1989, which was two double strength tablets a day, was much higher than needed. Bactrim given only three times a week is equally effective.

It is worth quoting the following passage from the CDC recommendations.

"In 1989, the United States Public Health Service convened a Task Force of experts to consider the expanding knowledge base about prevention of Pneumocystis carinii pneumonia (PCP) among adults and adolescents (greater than or equal to 13 years of age) with human immunodeficiency virus (HIV) infection. This Task Force concluded that the morbidity, mortality, and cost due to PCP could be substantially reduced by appropriate use of antipneumocystis prophylaxis in subgroups of HIV-infected patients known to be at high risk, and developed recommendations for the administration of prophylactic regimens."

At this time 30,534 people in the US had already died of PCP.

Michael Callen was a patient of mine. He was tireless in his advocacy that recommendations be promoted to use measures to prevent PCP in people with AIDS. Michael was also one of the authors of the Denver Principles, which in his words essentially state "People with AIDS should have a say in any decision-making process that will affect our lives". He tried to do this with respect to PCP prophylaxis.

Michael with other activists met Dr Fauci in May of 1987, Michael was insistent in asking for recommendations to prevent PCP in people with AIDS. Michael wrote the following in relation to this meeting:

"It is particularly galling to me that 16,929 of the 30,534 unneccessary PCP deaths occurred since May of 1987, the date on which I and other AIDS activists met with Dr. Anthony Fauci (the closest person we have to an AIDS czar) to ask him - no, to *beg* him - to issue interim guidelines urging physicians to prophylax those patients deemed at high risk for PCP. He steadfastly refused to issue such guidelines. His reason? No data. As a result many more people died of PCP who didn't have to".

Dr. Fauci wanted data from a clinical trial of Bactrim for PCP prophylaxis in AIDS before he would recommend its use. But people were dying of PCP at a terrifying rate; I and some other physicians could not wait for these recommendations. I was routinely prescribing Bactrim, or another drug, dapsone to patients I deemed to be at risk for PCP.

I was fortunate in that I had some experience in the 1970s dealing with infections in people who had received kidney transplants. These individuals are intentionally immunosuppressed, to avoid rejection of the transplanted kidney, and because of that immunosuppression, they experience a number of the same opportunistic infections seen in AIDS, including PCP. They also can sometimes get Kaposi's sarcoma. As an infectious diseases specialist, with some experience in the transplantation field, I was familiar from the beginning of the epidemic with the use of Bactrim to prevent PCP.

I found it remarkable that at some transplant centers patients received PCP prophylaxis without the need for a trial while people with AIDS were denied this intervention. There had been several trials of PCP prophylaxis in different transplant populations at various times. But after Walter Hughes demonstrated the efficacy of bactrim in 1977, the need for these trials is debatable. I don't know if anyone has written a history of the use of PCP prophylaxis following Dr. Hughes 1977 trial. I feel fairly certain that in groups at risk for PCP other than the leukaemic children studied by Dr Hughes, Bactrim use has been erratic, with some receiving the intervention, maybe just following the criteria suggested by Dr. Hughes himself in 1981 (where the PCP recurrence rate is at least 15%), while other groups had to wait for the results of trials before receiving the benefit.

In the case of AIDS a trial of Bactrim prophylaxis was finally conducted by Margaret Fischl in patients with Kaposi's sarcoma, using two double strength tablets a day. At this dose adverse reactions were seen, but only 5 (17%) of patients had to discontinue treatment. As already noted we soon learned how to reduce the frequency of these reactions by desensitization procedures and using a much reduced dose.

The CDC recommendations did note that the trial was conducted in patients with Kaposi's sarcoma, and in a typically pedantic and ultimately absurd fashion, warned us that there was no evidence that prophylaxis would be effective in AIDS patients without Kaposi 's sarcoma. They thankfully stopped short of demanding a trial in AIDS patients without Kaposi's sarcoma.

In the early days of the epidemic we could not know which patients were at risk for PCP. We had to learn that 200 CD4 cells was the dangerous threshold, below which there was a substantial risk of infection. But well before this we were perfectly able to target a population at great risk for PCP: these were people who had experienced one attack already. They were almost certainly going to experience another one but their protection was not considered to be a matter of urgency by the federal AIDS medical leadership. Of course in the absence of effective treatments for HIV disease, preventing PCP would have been a life extending rather than a life saving intervention.

Another curious and indefensible objection to PCP prophylaxis was raised by Dr Samuel Broder who was then head of the National Cancer Institute. He felt it justifiable to *discourage* the use of PCP prophylaxis on the grounds that the introduction of AZT would make this practice redundant! This objection was raised in the complete absence of any evidence that AZT could prevent PCP in a significant and durable fashion, if at all.

Michael Callen promoted PCP prophylaxis in other ways.

He was the President of the PWA Coalition in New York City (PWAC), and the founding editor of the PWA Newsline. Michael did what he could to bring attention to the need for PCP prophylaxis in the PWA Newsline. He also did so in two volumes published by PWAC - Surviving and Thriving with AIDS.

Around 1987 feeling so frustrated at the wilful neglect of PCP prophylaxis by so much of the medical establishment, I wrote a one page article for the Newsline. I remember the occasion quite well as neglect of PCP prophylaxis was something Michael and I often discussed. During one of these discussions, out of frustration, I grabbed a piece of paper at my New York apartment and wrote about PCP prophylaxis for the PWAC Newsline. It probably took me less than ten miniutes with Michael standing behind me. It was published unchanged.

Here is a reproduction of that article and also a later one, both for the PWA Newsline.

The road to PCP prophylaxis was already long and troubled, but had one further detour to make, an expensive distraction with aerosolized pentamidine lasting four to five years. Pentamidine is another drug used to treat PCP for years before the AIDS epidemic was first recognized. In fact, when it was needed before AIDS began, it had to be requested from the CDC where the stocks were kept. One indication that AIDS cases were appearing at the beginning of the 1980s was awareness at CDC that there were increasing numbers of requests for pentamidine, meaning that there were more cases of PCP. Pentamidine is given by intravenous injection and has significant toxicity. It was hoped that this toxicity could be avoided by delivering the drug directly to the lungs by aerosol inhalation. The droplet size was important if the drug was to reach the parts of the lung where the organism proliferated. So much time was initially spent in studying nebulizers of different design. Two types competed - an ultrasonic mechanism for delivering droplets and one in which the aerosol was produced by a nebulizer using compressed air. Then trials of its safety and efficacy were needed. In 1987 two trials were conducted by two community research organizations. The Community Consortium in San Francisco provided efficacy data, and the Community Research Initiative (CRI) in New York provided the safety data required by the FDA in the approval process. I wrote the protocol and was the principal investigator for the New York study, which was funded by Lyphomed, the company that manufactured pentamidine for aerosol use.

Pentamidine for injection was available as a generic preparation. The formulation for aerosol use however was not and so was costly in the US. Another organization that Michael Callen, Tom Hannan and I had organized to distribute egg lipids - AL721, (an interesting topic itself, perhaps for another post)the PWA Health group, imported a cheaper version from the UK.

A number of physicians treating people with AIDS set up inhalation machines in their offices.

Here is what it looked like. The picture was taken during the CRI trial.

Aerosolized pentamidine proved to be inferior to Bactrim as a prophylactic agent and was associated with unusual complications. It presented environmental hazards as other organisms - such as TB could be disseminated, and also resulted in the occurrence of pneumocystis infections in organs other than the lungs.

In all likelihood aerosolized pentamidine was pursued as a possible PCP prophylactic agent because interest in Bactrim was so discouraged by the federal medical leadership.

It is not irrelevant to note that unlike pentamidine for use as an aerosol, Bactrim was available as an inexpensive generic preparation.

Should there be interest in a longer and referenced account of this curious episode in the medical response to AIDS, which also tries to find some explanation for the long delay in providing patients with a simple life extending intervention the following link will lead to a more detailed article written in 2006.
