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Musings on Penicillin: Can We Learn from History?

By David Shlaes — January 22, 2019

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Lately, I've been thinking about new approaches to antibacterial therapy. But I keep going back to some old family history.

It was 1944. My father was completing his internship year in New York City. That summer, he took on additional work as a physician for a childrens' camp in Connecticut. My aunt, who suffered from type 1 diabetes, came to visit. Her parents thought the fresh air and activity would help. Soon after arriving, she developed a staphylococcal breast abscess. My father tried treating her with sulfonamides, but her condition deteriorated rapidly.

She was hospitalized in Manhattan delirious with positive blood cultures. The family gathered, arriving from Chicago, thinking she would not survive. My father knew that penicillin was available for use in our troops fighting overseas and he had heard that the army would supply the drug for emergency use through public health offices around the country. He called the public health commissioner for the City of New York and was able to obtain penicillin for my aunt. With intravenous penicillin, she recovered rapidly. She lived another 25 years before succumbing to cardiovascular disease complicating her diabetes.

During the bad old days of the FDA meltdown (starting around 2000, accelerating in 2006 and reversed by 2012), we used to speculate whether penicillin could even be developed and approved today. I think that for intravenous penicillin in 1945 the answer is a resounding yes. But for oral penicillin – the answer is maybe. For oral penicillin, what clinical indication could one study?

The requirements to study very severe skin and soft tissue infections might preclude the use of an oral drug. Clinical trials in pneumonia might work, though. For streptococcal pharyngitis, the FDA

guidance has been withdrawn. Then, imagine if we did not know about the frequency of hypersensitivity reactions to penicillins (as we might not have known in 1944-5). After marketing penicillin we realize that about 1 in 7000 treated patients develop a serious allergic reaction and death occurs in 1 in 67,000 to 1 in 70,000 treated patients (Idsoe O, Guthe T, Sillcox RR, de Weck AL. Nature and extent of penicillin side-reactions with particular reference to fatalities from anaphylactic shock. Bull World Health Organ 1968; 38: 159–88 – see this link [1]).

What would happen then? I presume that intravenous penicillin approved for serious infections would remain approve with some warning label. But oral penicillin would probably be restricted to the treatment of pneumonia and approval withdrawn for other indications.

One question I have asked my friends at FDA is – how was penicillin approved in 1945? I don't yet have a clear answer. Apparently this information is very hard to find – especially in the midst of our current government shutdown. But I believe that we will find that the approval of penicillin was based on published papers including experiences such as I described above. In that case, this is, in part, like approving a drug based on external controls where all clinicians can agree that the treatment effect is very large.

I also think that this is a principle we should consider today for new therapies that have obvious dramatic ameliorative effects in otherwise deadly circumstances. Case examples can be found among patients treated for severe, antibiotic-resistant sepsis with custom-designed bacteriophage cocktails (e.g. Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J, Lessor L, Barr JJ, Reed SL, Rohwer F, Benler S, Segall AM, Taplitz R, Smith DM, Kerr K, Kumaraswamy M, Nizet V, Lin L, McCauley MD, Strathdee SA, Benson CA, Pope RK, Leroux BM, Picel AC, Mateczun AJ, Cilwa KE, Regeimbal JM, Estrella LA, Wolfe DM, Henry MS, Quinones J, Salka S, Bishop-Lilly KA, Young R, Hamilton T. Antimicrob Agents Chemother. 2017 Sep 22;61(10). pii: e00954-17. doi: 10.1128/AAC.00954-17 – see this link [2]).

This case example is complicated by the use of concomitant antibiotics and the emergence of bacteriophage resistance during therapy. And these sorts of complicating issues may also undermine our belief that the miraculous clinical improvement seen in this case was due to the bacteriophage therapy. Treatment today is so much more complicated that it was in 1944-5. Nevertheless, those taking care of the patient in this example remain convinced that bacteriophage therapy was in large part responsible for this patient's survival just as my father was sure that penicillin cured my aunt.

Another observation from my musings is that whatever the new therapy is that we contemplate, its clinical effect must be dramatic and measurable in a way that convinces clinicians (and regulators) that it is a valuable addition to our treatment paradigm. This remains our challenge. Would it also be a challenge for penicillin if it were to be developed today as one of the first antibiotics?

(I apologize if it seems like these considerations are circular and go on forever - but I thought I would share anyway).

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