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Limitations of beta-lactam therapy for infections caused by susceptible Gram-positive bacteria

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Summary Penicillin and related beta-lactam agents have been the most widely used and most important antimicrobials in medical history, and remain the recommended therapy for many infectious diseases 85 years after the discovery of penicillin by Alexander Fleming. Yet the efficacy of these agents has been undermined by two factors — the emergence of clinically significant resistance to the antimicrobial activity of these agents, and clinical situations in which these drugs may be suboptimal (even though the bacterial pathogens are not "resistant" to the drugs). Observations in experimental infection models in animals (group A streptococcal myositis, pneumococcal meningitis and pneumonia, group B streptococcal sepsis) and in some cases clinical studies suggest that monotherapy with beta-lactam antibiotics may be inferior to treatment with other types of antibiotics, alone or in combination with beta-lactams — even in situations where the bacterial pathogens remain fully "susceptible" to beta-lactams *in vitro*.

Introduction

The discovery of penicillin by Alexander Fleming[1] and the demonstration by Howard Florey and Ernst Chain at Oxford that penicillin was effective for the treatment of systemic bacterial infections in mice[2] led to the development of penicillin as the first "miracle drug". These landmark achievements in the history of medicine were honored by the 1945 Nobel Prize in Physiology or Medicine.[3] More than eight decades after its discovery, penicillin remains a remarkably useful antibiotic, the preferred agent to treat ailments ranging from streptococcal pharyngitis to syphilis. Subsequently, the development of semi-synthetic penicillins and then the cephalosporins have made the beta-lactam antibiotics the most valuable antimicrobial agents in medical history.[4]

Yet within a few years of the development of penicillin, two limitations of this agent were apparent: potential for the development of resistance[5] and poor efficacy of the

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antibiotic in some clinical situations involving a high bacterial inoculum,[6] even in the lack of apparent "resistance". Subsequently, these same limitations have been observed with newer beta-lactams. The development and implications of clinically significant antimicrobial resistance in bacteria, predicted by Rene Dubos and other microbiologists,[7] has been the subject of intense study and commentary. The limitations of beta-lactam antibiotics in certain clinical settings (in the absence of antimicrobial resistance) have received considerably less attention — and will be the subject of this commentary.

The "Eagle Effect" — penicillin fails in the treatment of severe group A streptococcal soft tissue infections in mice

The first indications that penicillin therapy could fail in certain clinical situations came from the pioneering studies of penicillin therapy of experimental group A streptococcal infections in mice performed by the American pathologist, Harry Eagle. As Eagle noted in 1952, in the introduction to his classic study "Experimental Approach to the Problem of Treatment Failure with Penicillin, I. Group A Streptococcal Infections in Mice"[6]: "Even large doses of penicillin continued for long periods of time may sometimes fail to cure in infections caused by organisms which, judged by their *in vitro* sensitivity, should have been controlled". In that landmark paper, Eagle showed that penicillin failed to cure severe group A streptococcal myositis in mice when either a large bacterial inoculum was used or bacteria were allowed to proliferate to a high concentration in tissue before the antibiotic was administered.[6] Almost 4 decades later, Dennis Stevens and colleagues confirmed Eagle's observations in a similar mouse model of group A streptococcal myositis – and demonstrated that certain non-beta lactam antibiotics (including the protein synthesis inhibitor, clindamycin) remained effective at high bacterial concentrations, unlike penicillin.[8] This "Eagle Effect" also is observed in other experimental infections (e.g., clostridial myonecrosis).

Is the "Eagle Effect" relevant to the treatment of humans with severe group A streptococcal soft tissue infections? By 1997, limited data suggested that treatment of necrotizing fasciitis caused by group A streptococcus with regimens including antibiotics other than beta-lactams might be superior to beta-lactam therapy alone, leading the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics ("Red Book Committee") to make this recommendation for the first time in the 24th edition, published in 1997: "Clindamycin, given intravenously, may be particularly beneficial in the treatment of some of these (invasive group A streptococcal) infections, such as necrotizing fasciitis and toxic shock syndrome, and is recommended by some experts in addition to penicillin G".[9]

The following year, in 1998, Stevens and colleagues published their data comparing clindamycin and penicillin therapy in the mouse model of group A streptococcal myositis.[8] Then, in 1999, Jim Todd and colleagues in Denver published a retrospective case series summarizing the outcomes of children with invasive group A streptococcal infections – reporting an 83% favorable outcome of superficial GAS infections in children when these infections were initially treated with protein synthesis inhibitors ± a cell wall inhibitor (beta-lactam antibiotic) versus a 48% favorable outcome after treatment with cell wall inhibitors alone.[10] Most of the children in this cohort had deep-seated soft tissue infections. Subsequently, the authors of the 25th Edition of the Red Book, published in 2000, made the recommendation for addition of a protein synthesis inhibiting antibiotic such as clindamycin more explicit. For the treatment of "severe invasive group A streptococcal infection" (including necrotizing fasciitis AND streptococcal or staphylococcal toxic shock syndrome), "parenteral antimicrobial therapy at maximal doses for age, to kill organisms with bactericidal cell wall inhibitor and stop enzyme, toxin, or cytokine production with protein synthesis inhibitor (e.g., clindamycin)" was recommended.[11] The most recent (29th) edition of the Red Book, published in 2012, continues to recommend the addition of a protein-synthesis inhibiting antibiotic such as clindamycin for treatment of necrotizing fasciitis and/or toxic shock syndrome and notes that clindamycin is "more effective than penicillin alone for treating well-established group A streptococccal infections" because "the antimicrobial activity of clindamycin is not affected by inoculum size, has a long post-antimicrobial effect, and … suppresses the synthesis of M– protein and bacterial toxins".[12] In Europe, the 2011 edition of the Blue Book recommends that "established (invasive) group A streptococcal infection is treated with a combination of a benzylpenicillin and clindamycin, which suppresses synthesis of bacterial toxins and M proteins.[13] The Blue Book also recommends clindamycin and/or a glycopeptide for serious infections caused by PVL-producing strains of *Staphylococcus aureus*, for similar reasons.

Though the clinical evidence for the benefit of clindamycin in patients with necrotizing fasciitis and other severe group A streptococcal infections was initially limited, subsequent experience has confirmed the value of adding clindamycin to beta-lactam antibiotics in the treatment of severe invasive group A streptococcal infections, including the extensive experience of Jonathan Carapetis and colleagues in Australia.[14]

It is likely that multiple mechanisms account for the Eagle effect, and a list of potential mechanisms can be gleaned from the Red Book and Blue Book guidelines quoted above.[10–13] Beta-lactam antibiotics have reduced activity against stationary phase bacteria, and the reduced expression of penicillin-binding proteins by stationary phase GAS may contribute to the failure of beta-lactams in necrotizing fasciitis.[15] The activity of clindamycin is largely independent of inoculum size and includes a long post-antibiotic effect. Unlike beta-lactams, protein synthesis inhibiting antibiotics also reduce the production of bacterial virulence factors and toxins (e.g., M protein, pyrogenic exotoxins).[16] As Nau and colleagues have noted, modulation of the release of proinflammatory bacterial components may also play a critical role (e.g., rapid release when exposed to cell-wall-active, lytic antibiotics such as the beta-lactams).[17] The magnitude and kinetics of the production and release of bacterial components affects the host inflammatory response to bacteria, and certain antibiotics