Double Gram-Positive Coverage for Acute Bacterial Skin and Skin Structure Infections: Has the Eagle Landed?

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In 1952, Harry Eagle discovered that penicillin was far less effective in high-inoculum streptococcal infections, specifically group A Streptococcus (GAS) [1]. Certain strains of streptococcal and staphylococcal species have demonstrated paradoxically reduced activity in higher concentrations vs lower concentrations of penicillin. This phenomenon is often described as the "Eagle effect" and has led to examination of non–cell wall modifying agents, such as protein synthesis inhibitors, for empiric and definitive therapy in these infections.

One of the major challenges of many known in vitro effects is determining whether or not and to what degree they translate clinically. Some of these include pharmacodynamic targets for antimicrobial effectiveness, clinical impact of toxin inhibition, and antimicrobial synergy and/or antagonism between select combination therapies.

Clindamycin, a protein synthesis inhibitor, is often used in combination with high-dose penicillin therapy for necrotizing skin and skin structure infections due to Streptococcus pyogenes. Recently, 2 observational studies have demonstrated decreased mortality of invasive GAS infections when clindamycin was used adjunctively in the management of these patients [2, 3]. The benefit is likely due to toxin inhibition, which previously had been demonstrated primarily through in vitro and animal studies. The 2011 Infectious Diseases Society of America clinical practice guidelines on methicillin-resistant Staphylococcus aureus (MRSA) do not routinely recommend protein synthesis inhibitors in the management of invasive MRSA disease, although some experts utilize this practice for infections such as necrotizing pneumonia [4]. The use of clindamycin as adjunctive therapy in the treatment of hospitalized acute bacterial skin and skin structure infections (ABSSSIs) is not currently recommended in adults. Vancomycin monotherapy is the most commonly used antimicrobial treatment in conjunction with incision and drainage if an abscess is present. However, the empiric use of combination gram-positive therapy (eg, 2 agents) for treatment of ABSSSIs could have far-reaching stewardship implications. With >600 000 hospital discharges annually in the United States, ABSSSI remains the most common presentation of MRSA infection.

In this issue, Wargo et al present intriguing data comparing vancomycin monotherapy to vancomycin plus clindamycin combination therapy for both hospital length of stay (HLOS) and 90-day readmissions [5]. Although HLOS was not different between the groups, it was reduced in patients receiving combination therapy (at least 48 hours) who presented with an abscess, not surprisingly MRSA being the most common pathogen. Readmission rates were also significantly lower in those patients receiving combination therapy. Some limitations include single-center study, low overall numbers of readmissions, and documentation of degree of critical illness such as intensive care unit stay or presence of bacteremia.

Vancomycin, because of its cell wall activity, could potentially produce lower overall clinical cure in high inoculum infections compared with protein synthesis inhibitors. Therefore, “double coverage” empirically with a ribosomal inhibitor such as clindamycin may provide additional clinical benefit, especially in critically ill patients or those with high-inoculum infection. Although clindamycin monotherapy is often used in pediatric patients, caution should be given in adults as diverse geographical differences in susceptibility exist, making empirical coverage not optimal in some areas of the United States. The likely increased risk of Clostridium
difficile with clindamycin relative to other common agents used for ABSSSIs (eg, vancomycin) is an important point to consider. Although no cases of C. difficile infection (CDI) were found in this analysis, it is unknown if patients may have presented to a different healthcare access point for treatment of CDI. The benefit of other protein synthesis inhibitors, such as doxycycline, is unknown but of interest due to potentially decreased risk of C. difficile acquisition [6]. Another potential option could be linezolid monotherapy, which has demonstrated improved clinical cure compared with vancomycin in one subset analysis of MRSA patients for complicated skin and soft tissue infections [7].

Reduced 90-day readmissions with empirical combination therapy of vancomycin plus clindamycin compared with vancomycin monotherapy in the Wargo et al study was also an interesting finding. However, definitive antimicrobial therapy may correlate more directly with 90-day readmission rates. The 3 most common discharge antibiotics were trimethoprim-sulfamethoxazole, clindamycin, and doxycycline, respectively. The optimal definitive antibiotic therapy is unknown and, as evidenced by the study, varies widely by prescriber, which occurs often in clinical practice. Definitive antimicrobial selection is often based on a number of different variables including patient allergies, drug interactions, host comorbidities, and prescriber preference as opposed to strong clinical evidence. Patients receiving combination therapy were much more likely to receive clindamycin as part of their home regimen (39% vs 15.5%). Interestingly, the combination group received nearly 2 fewer days of discharge antimicrobial therapy (8.6 days vs 10.2 days), reinforcing the stewardship principle that shortened durations of therapy in ABSSSIs after definitive incision and drainage remains prudent. Although 90-day readmission rates were significantly different, it is not known how many patients in each group accessed other points in the healthcare setting (eg, primary care provider’s office) for further treatment of their ABSSSI.

The paucity of data regarding management strategies of ABSSSI in the emergency department is an important limitation in current practice. Specific areas of need include predictors of admission as well as recurrence, which is a hallmark of ABSSSIs, in particular, abscesses due to S. aureus. Research is currently ongoing to delineate the role of the newly approved long-acting agents dalbavancin and oritavancin, which may offer the unique benefit of preventing admission to the hospital for ABSSSI management.

Antimicrobial stewardship is best defined as using the narrowest therapy possible to obtain optimal clinical outcomes while minimizing adverse effects [8]. For most infections, this should be accomplished through monotherapy. Examination of cell wall–active agents plus protein synthesis inhibitors deserves a randomized, double-blinded, multicenter investigation. Other protein synthesis inhibitors such as tetracyclines or oxazolidinones should be evaluated as well. Therefore, although using combination therapy for invasive streptococcal and staphylococcal infections is not an alien concept, the eagle has not quite yet landed for empirical coverage for hospitalized patients with ABSSSIs.

Note

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