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Review Article

Review of cephalosporin's role in *enterococcal* bacteremia infection

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ABSTRACT

Enterococci remains is one of the most common pathogens to cause nosocominal infections and nosocominal bacteremia in the United States. Due to emerging bacterial resistance, enterococci are feared nosocomial pathogens that can be challenging to treat.There is always a need to study regimens studied supporting alternative regimens due to this resistance. This review compared available data on cephalosporin synergistic combinations as alternative to aminoglycosides mainly in endocarditis, and evaluated their clinical potential use. The review included 6 studies (3 retrospective cohort studies, one surveillance one review article and one pilot study). The use of ampicillin and ceftriaxone combination could be a possible option in patients that are infected by HLAR strains and pose great contraindication to aminoglycoside use. More studies, specifically RCTs could make a clear-cut finding of what combination to use and for how long.

Key words: *Cephalosporin, Enterococci, Bacteremia, Endocarditis and E. Faecalis.*

BACKGROUND

Enterococci are Gram-positive, catalase-negative, non-spore-forming, facultative anaerobic bacteria, which usually inhabit the alimentary tract of humans in addition to being isolated from environmental and animal sources. Virulence factors of enterococci include the extracellular protein (Esp) and aggregation substances (Agg), both of which aid in colonization of the host. Before they were assigned their own genus, they were known as group D streptococci.[1]

Recent National Nosocomial Infection Surveillance (NNIS) surveys, revealed that enterococci remain as one of the three most common pathogens to cause nosocomial infections and the third most common cause of nosocomial bacteremia in the United States.[2,6] These infections commonly include urinary tract infections, followed by intra-abdominal and pelvic infections. In addition to rare, but severe infections such as surgical wound infections, bacteremia, endocarditis, neonatal sepsis and meningitis. These infections typically occur in very ill debilitated patients within the health care system. Enterococcus includes more than 17 species. Two of them; Enterococcus faecalis and Enterococcus faecium are the most commonly identified species accounting for more than 90% of clinical isolates. Additionally, 90% of enterococcal endocarditis cases are caused by E. faecalis and less than5% by E. faecium.[3,4]

With increasing antibiotic resistance, enterococci are recognized as feared nosocomial pathogens that can be challenging to treat.[7]

A major reason why these organisms survive hospital environment; is the intrinsic resistance to several commonly used antibiotics -having the penicillin-binding proteins and using already formed folic acid resulting in the resistance of both beta lactams and TMP-SMZ- and, perhaps more importantly, the acquired resistance this organism develops to most currently available antibiotics –including chloramphenicol, tetracyclines, rifampin, fluoroquinolones, aminoglycosides (high levels), and vancomycin - either by mutation or foreign genetic material receipt through the transport of plasmids or transposons.[4]

The morbidity and mortality of enterococcal endocarditis is high owing to the fact that 42% of patients require cardiac surgery and 29% had a 1-year mortality rate that has not changed in the last 3 decades if not increased.[3] Furthermore, enterococci with high level aminoglycoside resistance (HLAR), lactamase production and glycopeptide resistance including vancomycin resistant enterococci (VRE) have presented a therapeutic challenge to physicians due to the ease of acquiring and transferring antimicrobial drug resistance.[4,5,8]

Therefore, the need of different regimens and studies supporting these regimens is mandated to reduce these numbers. And

alternatives should be extensively studied and become more available due to this organism's accelerating resistance. In this review we will evaluate the studied use of cephalosporin, if any, in the treatment of enterococcalbatremia.

DATA SOURCE

A literature search was conducted using Medline/Ovid (1946-present, Aug 3 2016) and Embase (1980-2016). The following key words were used: Cephalosporin, Ceftriaxone, Enterococci, Bacteremia, Endocarditis and E. Faecalis. In addition, eligible articles were included and so were any available review articles in the matter.

Due to the limited available data, the search was not limited to clinical trials, however (1) case reports and (2) animal –in vitro- studies were excluded. Studies that were included were (1) English language and (2) Comparison studies. The initial search yielded 43 studies. After excluding non-relevant studies, case reports, in vitro studies and repetitive studies; we included 6 studies including 3 retrospective cohort studies, one surveillance one review article and one pilot study.

LITERATURE REVIEW

1) Guidelines Review:

The American Heart Association (AHA) guidelines have not modified their antibiotic recommendations on non-HLAR strains for almost 60 years, and although this has been the standard regimen for all these years, no randomized clinical trials supported the current evidence.[6] The combination of a beta lactam antibiotic with an aminoglycoside has proven to increase enterococcal cell membrane permeability in vitro, and since then, the empirical use of ampicillin and gentamycin has been the mainstay of treatment.[7,9] The latest AHA guidelines maintain the use of penicillin or ampicillin (or vancomycin in case of beta-lactam allergy) plus gentamicin as the combination of choice for E. faecalis infective endocarditis (EFIE) caused by non-HLAR strains.6AHA and European Society of Cardiology (ESC) guidelines do consider ampicillin plus ceftriaxone administration for at least 8 weeks a potential antibiotic therapy for EFIE with HLAR to both streptomycin and gentamicin.

Moreover, the recommended length of treatment has alsobeen consistent since the 1980s, which consists of a 4 week regimen for those with uncomplicated native valve endocarditis and a 6 week regimen for those with prosthetic valve endocarditis patientswith>3-month history of symptoms prior to diagnosis.The gentamicin dose schedule (3 mg/kg per 24 hours IV or IM in 3 equally spaced doses) has also remained unchanged for 2 decades.[6,10]

2) Synergistic Effect Between Amoxicillin and Low Level Cefotaxime

A new approach recommended and was studied in vitro and recently in vivo, within the past years has suggested the use of other combinations that included ceftriaxone instead of aminoglycosides. The basis for these reports was an in-vitro study that was conducted by Minardi et al., that proved a synergistic effect between amoxicillin and low level cefotaxime (a third-generation cephalosporin) against several High Level Gentamicin-Resistant (HLGR) and Non-High Level Gentamicin-Resistant (N-HLGR). The proposed mechanism of synergy was the partial saturation of penicillin binding proteins 4 and 5 by amoxicillin, and complete saturation of penicillin-binding proteins 2 and 3 by cefotaxime.[11,12,13,15]

3) Comparing Ampicillin with Ceftriaxone (AC) Vs Ampicillin with Gentamicin (AG)

A study that was carried out in Spain and Italy, byFernández-Hidalgo et al, investigated both efficacy and safety of ampicillin plus ceftriaxone (AC) in the treatment of E. Faecalis Infective Endocarditis (EFIE),14Gavaldà et al proved the initial proposed efficacy of the combination in a multicenter, open-label study that evaluated 43 patients with EFIE (49% with HLAR strains and 51% non-HLAR strains) treated with ampicillin with a dose of 2 g/4 h and ceftriaxone 2 g/12 h. Clinical cure rates were 71% and 73%, respectively, with 5% relapses.13The Fernandez study was an observational, nonrandomized, comparative multicenter, cohort study, in 17 hospitals (one was in Rome and the rest were on different locations in spain). Ampicillin was administered as 2g IV every 4 hours (with renal function adjustment as necessary) and Ceftriaxone was administered as 2g IV every 12 hours and finally, Gentamycin was administered as 3mg/kg/day (with renal function adjustment as necessary) and administered in 1, 2, or 3 divided doses and renal function at diagnosis (depending on the administering physician). Gentamycin trough levels were targeted between (0.5-1 mg/L) for multidose administration. Results showed that during the study period a total of 291 patients were treated. 159 (55%) with AC (patients had both HLAR and non-HLAR starains) and 87 (30%) with AG (Only non-HLAR starins) and the rest (15%) with other antibiotics. Overall median age was 70 years old and 206 (71%) were male.[14,16,18,19]

Overall, no differences were found between the AC and AG groups in terms of treatment failure, mortality during treatment or at 3 months of follow-up, and relapses. However, a higher number of patients (23% compared to 0% P<0.001) receiving ampicillin plus gentamicin switched or stopped gentamicin because of renal failure, even though more patients in the AC group had chronic renal failure at baseline (P=0.004), and although an outcome analysis based on the presence of HLAR was not performed, ampicillin plus ceftriaxone proved effective in both strains and was proven safer than the AG for a course of 4 to 6 weeks.

Both studies are subject to limitations. The most important limitation is the fact that none of them are Randomized Controlled Trials. The study by Gavalda et al is also limited by the small sample size; therefore, the results need to be interpreted with caution. Moreover, Fernández-Hidalgo et al's study group was mostly retrospectively collected. Additionally a potential bias of treatment regimen selection depending on patient's baseline renal function and the decision on which physicians stopped the AG regimen and switched the patient on something else. For example; 10 patients were given Ceftriaxone after a median length of 15 days receiving AG, and

therefore the recovery rate of the AC group could've been induced by this initial course of gentamicin. Another point woth mentioning is the incoherent schedule of gentamicin, and lack of tough level monitioring in some hospitals, that could've lead to those numbers of renal failure that was not assessed with glomerular filtration rate. Referral bias was also a major factor that could've affected the Fernández-Hidalgo et al study. At last, there was no documentation of long term side effects that occur after treatment discontinuation and it is known that long term cephalosporin treatment could cause C. Difficilesuperinfection or late infection, and the additional risk of developing VRE.[14,16,18,20]

4) The Use of Double Beta Lactam Combination for E. Faecalis Treatment:

Another pilot study, by G. Euba et al. that believes to be the first to evaluate a double beta lactam combination for the treatment of E. Faecalis orthopedic infections was conducted in Spain after the remission of one patient's endocarditis and vertebral osteomyelitis with the use of ampicillin-ceftriaxone combination.[17,18,20] Thirty-one patients were included in the study, 10 received the AC combination at a dose of 8 to 16g/day of ampicillin, and 2 – 4 g/day of ceftriaxone for a median duration of 25 days. Results showed that 25 patients (80%) had polymicrobial infections. 16 cases were excluded due to polymicrobial infection with AC resistant microorganisms (mostly Staphylococci and Pseudomonas aeruginosa) 1 case due to PCN allergy and 4 due to physician's preference. Baseline characteristics showed that 45% were male, median age was 69 years old. 9 out of 10 patients had their infection eradicated however one patient was superinfected due to S. aureus that required amputation. The pilot study presented some promising results of the bactericidal effect of AC combination, proposing an alternative path to those patients that are highly vulnerable to aminoglycoside's use, especially elderly patients with comorbidities. This study paves the way for better future well designed, comparative studies.[17,18,19]

5) Compared activity of 12 antibiotics alone and in combination, in vitro

Finally, C. Farina et al. compared the activity of 12 antibiotics alone, and in combination in vitro; against 27 E. faecalis strains isolated from blood culture in patients that had infective endocarditis.[22] This study was conducted in Italy and showed high in vitro activity of Daptomycin, Linezolid and Tigecycline when used alone. Additionally, a high synergistic effect was seen in fosfomycin-ceftriaxone combination with an inhibitory concentration FIC50:0.34, FIC90:0.78. Comparatively, ceftriaxone plus ampicillin showed more inhibitory concentrations of FIC50:0.66, FIC90:1.00. These results could have both of these relatively safe profile antibiotic regimens as alternative to aminoglycosides- ampicillin ones in selected patients. However In vivo studies are necessary to conclude the latter.[23]

CONCLUSION

The medical treatment of the enterococcal endocarditis, which could be rapidly bactericidal, is challenging due to the bacterial pattern of both intrinsic and acquired resistance. The exceeding rate of aminoglycoside enterococcal resistance has become a huge concern urging the availability of alternatives. This review compared available data on cephalosporin synergistic combinations as alternative to aminoglycosides mainly in endocarditis, and evaluated their clinical potential use.

In conclusion, it is important to investigate the presence or absence of HLGR strains of all cases of intractable enterococcal infections to make a decision of whether to use an AG combination or not. Despite the AHA and ESC guidelines that considered the alterative use of AC of at least 8 weeks, neither considered using this combination in non-HLAR EFIE. The Fernández-Hidalgo et al study promises an effectiveness of this combination for a shorter recommended course of only 6 weeks for both strains that excludes the need of prior identification of the strain of enterococci. Additionally, the use of this combination could be a possible option in patients that are infected by HLAR strains and pose great contraindication to AG use.

This review suggests that future RCTs could investigate the use of cephalosporins for enterococaal endocarditis. Such studies should look into possible combination of antibiotics, duration of treatment, safety, efficacy, and any possible pharmacoeconomic benefits of such combinations. Also updated guidelines should guide clinicians to any suggested treatment based on previously published data and results.

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