European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:419–422
https://doi.org/10.1007/s10096-018-03446-2

EDITORIAL

Infective endocarditis caused by *Streptococcus agalactiae*: time for beta-hemolytic streptococci to follow treatment recommendations for *S. aureus*?

Parham Sendi [1,2]

Published online: 24 January 2019

Infective endocarditis (IE) caused by *Streptococcus agalactiae* (group B *Streptococcus*, GBS) is a serious disease. Ivanova-Georgieva et al. [1] recently demonstrated the similarities and differences in the clinical characteristics of left-sided IE caused by GBS and *S. aureus*. Their results underscored the severity of GBS IE, confirming findings of prior studies [2, 3].

Discussion of the optimal antibiotic treatment for (native valve) GBS IE leads to the question of whether combination therapy with adjunctive gentamicin treatment is as effective as beta-lactam monotherapy. This question applies to IE caused by other beta-hemolytic streptococci, also [4]. In the study by Ivanova-Georgieva et al. [1], patients with GBS IE were treated with adjunctive aminoglycosides significantly more often (26 of 39 [66.7%]) than those with *S. aureus* IE (122 of 313 [39%], $p = 0.002$). In a recent study by El Rafei et al. [5] on IE caused by beta-hemolytic streptococci (49 cases, 39 [80%] of them caused by GBS), combination therapy was administered in 25 (58.1%) of 43 IE cases and beta-lactam monotherapy in 18 (41.9%). The proportion of patients treated with adjunctive gentamicin was understandable considering the IE recommendations in the European and US guidelines for IE [6, 7]. However, given the relatively small number of GBS IE cases in each of the published series [1–3] and the rarity of the disease [1], solid evidence to answer this question is unlikely to be generated in the near future. Therefore, it is worthwhile to review the data on this topic on historical, clinical, microbiological, and emotional levels.

In 2015, the authors of the European guidelines stated that "gentamicin should be given for 2 weeks" for IE caused by beta-hemolytic streptococci [6]. This recommendation was added to the 2009 guidelines without providing a rationale. In 2002, Lefort et al. [8] compared the antibiotic treatment for IE due to beta-hemolytic streptococci (56 cases, 34 [61%] of them caused by GBS) with that for IE due to *Streptococcus milleri*. Combination therapy with adjunctive gentamicin was given in 51 of 56 (91%) and 27 of 29 (93%) cases, respectively, which prevented the authors from drawing a conclusion on the treatment outcome with beta-lactam monotherapy. In 2015, the American Heart Association (AHA) recommended that clinicians should "consider" the addition of gentamicin to penicillin or ceftriaxone for at least the first 2 weeks of a 4- to 6-week course of antimicrobial therapy for group B, C, and G streptococcal IE [7]. The statement is referenced with two publications [9, 10] and in line with the 2005 AHA statement on IE [11]. While one of the two citations refers to the 1998 Infectious Diseases Society of America (IDSA) statement [9], the other points towards the publication of two case reports of IE due to group G *Streptococcus* and a literature review [10]. In their 1988 literature review, Smyth et al. [10] compared 20 IE cases treated with beta-lactam antibiotic alone or in combination with an aminoglycoside for less than 14 days with 12 IE cases treated with adjunctive aminoglycosides for 14 days or more. They also compared 22 IE cases with beta-lactam antibiotic alone or in combination with an aminoglycoside for less than 28 days with 10 IE cases treated with adjunctive aminoglycosides for 28 days or more. Although the analyses for complications or outcome revealed no significant differences, the authors supported the view that patients with group G streptococcal endocarditis should be treated with combination therapy for at least 28 days [10]. Overall, there are no clinical data demonstrating that combination therapy with adjunctive gentamicin is superior to beta-lactam monotherapy for IE caused by beta-hemolytic streptococci.

✉ Parham Sendi
Parham.Sendi@ifik.unibe.ch

[1] Institute for Infectious Diseases, University of Bern, Friedbühlstrasse, 51, CH-3001 Bern, Switzerland

[2] Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University Basel, Basel, Switzerland

Microbiological rationales behind the combination therapy are results from in vitro and animal experimental GBS infection studies suggesting synergism or a better bactericidal effect [5]. These studies were mainly initiated because of the worrisome mortality rates in neonates with GBS sepsis and meningitis before the implementation of intrapartum prophylaxis for GBS colonized women [12]. These studies suggested a trend towards faster killing of planktonic GBS in vitro, but remain inconclusive in vivo (Table 1). The definitions and methods used for synergism assessment vary and all have limitations. This again indicates the difficulty in transferring synergy assay results from the laboratory to patient treatment concepts. For example, the bacterial inoculum in time-kill experiments (e.g., 10^5–10^7 colony forming units [CFU]/mL) is up to 100,000 times higher than that found in human sepsis (e.g., 1–100 CFU/mL) [22]. The antibiotic concentrations administered to patients are significantly higher than those used in experimental assays (e.g., 0.5× to 4× the minimum inhibitory concentration [MIC]). Recently, performed time-kill assays indicated that the addition of gentamicin to penicillin contributes to faster killing of planktonic GBS without fulfilling the criteria for synergism. The in vitro effect of faster killing was seen only at low penicillin concentrations and only within the first few hours of the assay [23]. When human blood products (serum, neutrophilic granulocytes, or whole blood from healthy volunteers [≥ 65 years]) were added to experiments, no beneficial effect of adjunctive gentamicin was seen [24]. Thus, the available in vitro data and data from animal experiments on faster GBS killing or synergism do not justify prolonged gentamicin treatment in GBS IE.

Another microbiological rationale for combination therapy may be the higher penicillin MIC values of GBS in comparison to those of group A *Streptococcus*. The relevance of the penicillin MIC for implementing adjunctive gentamicin treatment has not been evaluated for beta-hemolytic streptococci. Viridans group streptococci and *Streptococcus gallolyticus (bovis)* are considered susceptible to penicillin when the MIC is ≤ 0.125 mg/L. According to the European guidelines and the AHA statement, IE caused by these microorganisms can be treated with adjunct gentamicin to shorten the total treatment duration from 4 to 2 weeks [6, 7]. Such a recommendation does not exist for beta-hemolytic streptococci. Only a small minority of GBS have a higher MIC than 0.125 mg/L (5 [0.15%] of 3261 GBS in European Committee on Antimicrobial Susceptibility Testing) [25].

In clinical practice, the tendency is to administer more and several antibiotics when a patient has severe disease. In our study with 74 GBS IE cases, a logistic regression analysis suggested that patients receiving aminoglycosides had a higher probability of developing heart failure than did those who did not receive them [26]. This indicated that aminoglycosides were given more frequently to patients with severe clinical manifestations of IE. Similarly, in the study by El Rafei et al. [5], combination therapy was significantly more frequently found in patients with an intra-cardiac abscess (10 of 25 [40%] versus 2 of 18 [11%] in the beta-lactam monotherapy group, $p = 0.030$). The study by Ivanova-Georgieva et al. [1] may help us to recall the previous treatment concepts of *S. aureus* IE in the absence of prosthetic valves, a disease that is as severe as GBS IE. In the 1980s, both right- and left-sided IE due to *S. aureus* were commonly treated with an antistaphylococcal penicillin for 4–6 weeks plus aminoglycosides for the first 2 weeks [27, 28]. Over the next years, trials comparing a cell-wall active agent with and without gentamicin demonstrated that combination therapy reduced the duration of bacteremia by approximately 1 day compared with monotherapy, but without reducing the mortality or frequency of cardiac complications [29]. The price for this effect was increased nephrotoxicity. In 2005, the AHA recommended the optional addition of gentamicin (3 mg/kg per 24 h IV/IM in 2

Table 1 In vitro and animal experimental GBS infection studies suggesting synergism or a better bactericidal effect before the implementation of intrapartum prophylaxis for GBS colonized women

Reference	Year	Study	Animals	Beta-lactam antibiotic	Aminoglycoside	Conclusion
[13]	1976	In vitro	–	Ampicillin or penicillin	Gentamicin	Faster killing with combination therapy
[14]	1977	In vitro	–	Ampicillin or penicillin	Kanamycin or gentamicin	Penicillin + gentamicin were bactericidal
[15]	1977	In vivo	Mice	Ampicillin or penicillin	Gentamicin	Faster killing with combination therapy
[16]	1979	In vitro	–	Ampicillin	Various aminoglycosides	Synergism with combination therapy
[17]	1981	In vitro	–	Penicillin	Gentamicin	Faster killing with combination therapy (experiments with 4 penicillin-tolerant GBS)
[18]	1981	In vitro	–	Penicillin	Gentamicin	Synergism with combination therapy
[19]	1982	In vivo	Mice	Ampicillin or penicillin	Gentamicin	Non-significant higher survival rate with combination therapy
[20]	1985	In vitro		Ampicillin or penicillin	Gentamicin	Faster killing with combination therapy
[21]	1987	In vitro In vivo	Rats	Penicillin	Gentamicin	Combination therapy was not more effective than monotherapy

or 3 equally divided doses) for the first 3 to 5 days of therapy for left-sided *S. aureus* IE [11]. With this adjunctive gentamicin regimen, significant renal dysfunction without additional clinical benefit for *S. aureus* IE treatment was observed in the following years [30, 31]. Current guidelines for staphylococcal native valve IE do not recommend gentamicin [6, 7].

Considering the lack of evidence for adjunctive gentamicin therapy in GBS IE and the clinical similarities of *S. aureus* IE and GBS IE, as shown by Ivanova-Georgieva et al. [1], it is time that the adjunctive gentamicin recommendation for the treatment of native valve IE caused by beta-hemolytic streptococci follow those for IE caused by *S. aureus*: The recommendation should be abandoned.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ivanova-Georgieva R, Ruiz-Morales J, Garcia-Cabrera E, Garcia-Lopez MV, Galvez-Acebal J, Plata-Ciezar A, de la Torre Lima J, Hidalgo-Tenorio C, Martinez-Marcos FJ, Garcia DV, Luque R, de Alarcon Gonzalez A (2018) Left-sided infective endocarditis caused by *Streptococcus agalactiae*: rare and serious. Eur J Clin Microbiol Infect Dis in this issue
2. Ivanova Georgieva R, Garcia Lopez MV, Ruiz-Morales J, Martinez-Marcos FJ, Lomas JM, Plata A, Noureddine M, Hidalgo-Tenorio C, Reguera JM, De la Torre Lima J, Galvez Aceval J, Marquez M, de Alarcon A, Andalusian Group for the Study of Cardiovascular Infections of the Andalusian Society of Infectious Diseases S (2010) Streptococcus agalactiae left-sided infective endocarditis. Analysis of 27 cases from a multicentric cohort. J Inf Secur 61(1):54–59
3. Sambola A, Miro JM, Tornos MP, Almirante B, Moreno-Torrico A, Gurgui M, Martinez E, Del Rio A, Azqueta M, Marco F, Gatell JM (2002) Streptococcus agalactiae infective endocarditis: analysis of 30 cases and review of the literature, 1962-1998. Clin Infect Dis 34(12):1576–1584
4. Blackberg A, Nilson B, Ozenci V, Olaison L, Rasmussen M (2018) Infective endocarditis due to Streptococcus dysgalactiae: clinical presentation and microbiological features. Eur J Clin Microbiol Infect Dis 37(12):2261–2272
5. El Rafei A, DeSimone DC, DeSimone CV, Lahr BD, Steckelberg JM, Sohail MR, Wilson WR, Baddour LM (2016) Beta-haemolytic streptococcal endocarditis: clinical presentation, management and outcomes. Infect Dis (Lond) 48(5):373–378
6. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, Document R, Erol C, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J, Walker DM (2015) 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 36(44):3075–3128
7. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA, American Heart Association Committee on Rheumatic Fever E, Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council (2015) Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 132(15):1435–1486
8. Lefort A, Lortholary O, Casassus P, Selton-Suty C, Guillevin L, Mainardi JL, beta-Hemolytic Streptococci Infective Endocarditis Study G (2002) Comparison between adult endocarditis due to beta-hemolytic streptococci (serogroups A, B, C, and G) and Streptococcus milleri: a multicenter study in France. Arch Intern Med 162(21):2450–2456
9. Baddour LM (1998) Infective endocarditis caused by beta-hemolytic streptococci. The Infectious Diseases Society of America's Emerging Infections Network. Clin Infect Dis 26(1):66–71
10. Smyth EG, Pallett AP, Davidson RN (1988) Group G streptococcal endocarditis: two case reports, a review of the literature and recommendations for treatment. J Inf Secur 16(2):169–176
11. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA, Committee on Rheumatic Fever E, Kawasaki D, Council on Cardiovascular Disease in the Y, Councils on Clinical Cardiology S, Cardiovascular S, Anesthesia, American Heart A, Infectious Diseases Society of A (2005) Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the committee on rheumatic fever, endocarditis, and Kawasaki disease, council on cardiovascular disease in the young, and the councils on clinical cardiology, stroke, and cardiovascular surgery and anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 111(23):e394–e434
12. Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, Hadler JL, Danila R, Cieslak PR, Schuchat A (2000) Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 342(1):15–20
13. Schauf V, Deveikis A, Riff L, Serota A (1976) Antibiotic-killing kinetics of group B streptococci. J Pediatr 89(2):194–198
14. Overturf GD, Horowitz M, Wilkins J, Leedom J, Steinberg E (1977) Bactericidal studies of penicillin-gentamicin combinations against group B streptococci. J Antibiot (Tokyo) 30(6):513–518
15. Deveikis A, Schauf V, Mizen M, Riff L (1977) Antimicrobial therapy of experimental group B streptococcal infection in mice. Antimicrob Agents Chemother 11(5):817–820
16. Cooper MD, Keeney RE, Lyons SF, Cheatle EL (1979) Synergistic effects of ampicillin-aminoglycoside combinations on group B streptococci. Antimicrob Agents Chemother 15(3):484–486
17. Kim KS, Anthony BF (1981) Penicillin tolerance in group B streptococci isolated from infected neonates. J Infect Dis 144(5):411–419

18. Baker CN, Thornsberry C, Facklam RR (1981) Synergism, killing kinetics, and antimicrobial susceptibility of group A and B streptococci. Antimicrob Agents Chemother 19(5):716–725
19. Needham JR, Altman DG, Whitelaw AG (1982) Ampicillin and penicillin compared for the treatment of experimental group B streptococcal septicaemia in mice. Med Lab Sci 39(3):271–274
20. Swingle HM, Bucciarelli RL, Ayoub EM (1985) Synergy between penicillins and low concentrations of gentamicin in the killing of group B streptococci. J Infect Dis 152(3):515–520
21. Kim KS (1987) Effect of antimicrobial therapy for experimental infections due to group B Streptococcus on mortality and clearance of bacteria. J Infect Dis 155(6):1233–1241
22. Rello J, van Engelen TSR, Alp E, Calandra T, Cattoir V, Kern WV, Netea MG, Nseir S, Opal SM, van de Veerdonk FL, Wilcox MH, Wiersinga WJ (2018) Towards precision medicine in sepsis: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect 24(12):1264–1272
23. Ruppen C, Lupo A, Decosterd L, Sendi P (2016) Is penicillin plus gentamicin synergistic against clinical group B Streptococcus isolates?: an in vitro study. Front Microbiol 7:1680
24. Ruppen C, Decosterd L, Sendi P (2017) Is gentamicin necessary in the antimicrobial treatment for group B streptococcal infections in the elderly? An in vitro study with human blood products. Infect Dis (Lond) 49(3):185–192
25. European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2018) Antimicrobial wild type distributions of microorganisms https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=−1&Specium=218 Accessed 26 Nov 2018
26. Sendi P, Ericsson M, Olaison L (2012) Infective endocarditis caused by group B Streptococcus: the role of aminoglycoside-combination. J Inf Secur 64(1):127–129
27. Bayer AS, Murray BE (2009) Initial low-dose aminoglycosides in Staphylococcus aureus bacteremia: good science, urban legend, or just plain toxic? Clin Infect Dis 48(6):722–724
28. Le T, Bayer AS (2003) Combination antibiotic therapy for infective endocarditis. Clin Infect Dis 36(5):615–621
29. Korzeniowski O, Sande MA (1982) Combination antimicrobial therapy for Staphylococcus aureus endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. Ann Intern Med 97(4):496–503
30. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, Levine DP, Chambers HF, Tally FP, Vigliani GA, Cabell CH, Link AS, DeMeyer I, Filler SG, Zervos M, Cook P, Parsonnet J, Bernstein JM, Price CS, Forrest GN, Fatkenheuer G, Gareca M, Rehm SJ, Brodt HR, Tice A, Cosgrove SE, Sa E, Bacteremia Study G (2006) Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 355(7):653–665
31. Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, Rupp ME, Chambers HF, Karchmer AW, Boucher HW (2009) Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 48(6):713–721