

RESEARCH ARTICLE

Epidemiology and Antimicrobial Susceptibility of Anaerobic Bloodstream Infections: A 10 Years Study

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ABSTRACT

Objective: The majority of patients with anaerobic bloodstream infections (BSIs) do not receive appropriate empirical antimicrobial treatment as this infection remains unsuspected on clinical basis. This study determines the incidence rate, the prevalence and antibiotic susceptibility pattern of anaerobes causing BSIs in East Sussex Healthcare Trust, England.

Methods: It is a retrospective study from July 2007 to July 2017. Demographic and laboratory data were collected on all microbiologically proven anaerobic BSIs.

Results: During the study period, 106,905 blood cultures were processed in the laboratory. A total of 324 anaerobic organisms were isolated from 312 blood cultures on 310 patients (167 males), representing a positivity rate of 0.30% of total blood cultures and 2.41% of total positive blood cultures (13,425). Approximately 76% (238 episodes) of anaerobic bacteremia occurred in >60 years old (236) patients. The admitting services were: emergency department (ED) (42%), medical (25%), surgical (16%) critical care unit (7%), and hematology (5%). The most frequent isolates were *Bacteroides spp.* (42%), *Clostridium spp.* (24%), and *Propionibacterium spp.* (9%). Polymicrobial bloodstream infections were recorded in 45 episodes. Amoxicillin/clavulanic acid, metronidazole, clindamycin remained most effective antibiotics against anaerobes with a sensitivity rate of 93%, 92%, and 81% respectively. Penicillin was least sensitive (43%) against anaerobes.

Conclusions: This study highlights a low rate of anaerobic bacteremia during 10 years with *Bacteroides spp.* as the predominant organism. This study also confirms that the empirical antibiotic therapy used in our hospital remains appropriate as more than 92% isolates were sensitive to amoxicillin/clavulanic acid and metronidazole. *J Microbiol Infect Dis* 2018; 8(4): 135-139

Keywords: Anaerobes, antibiotics, bloodstream infections, susceptibility

INTRODUCTION

Despite the low incidence of anaerobic bloodstream infections (4%) around the world, the mortality in anaerobic bloodstream infections has been reported between 20% and 38%. Anaerobic bloodstream infections are uncommon in the community and hospital patients. Anaerobic bacteria are usually considered as normal flora in various sites particularly over mucosal surface areas in the body. The anaerobes require anaerobic condition conditions (the absence of oxygen) to grow and they grow slowly as compared to aerobic organisms. One study from the United States reported the re-emergence of anaerobic

bacteremia. The isolation of anaerobes from blood cultures is usually associated with high mortality. Anaerobic bacteria can cause multiorgan failure [1-5]. Majority of patients with anaerobic bloodstream infections do not receive appropriate empirical antimicrobial treatment as this infection remains unsuspected on clinical basis [6]. One study investigated the impact of inappropriate therapy, such as delay in starting antibiotic or choosing the resistant antibiotic despite availability of the results, in anaerobic bloodstream infections on mortality rates. Higher mortality rate was recorded due to inappropriate antimicrobial therapy in this study [7]. Antibiotic susceptibility testing on anaerobic organisms is

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usually not carried out as it is technically difficult to perform, expensive and the results are available late because of slow growth of anaerobes. Some studies reported the rise in antimicrobial resistance in anaerobic organisms [8,9]. Adverse outcome in anaerobic blood stream infections is associated with the use of inappropriate therapy or delay in therapy or delay in the sensitivity results availability. The main objective of our study was to examine the prevalence and antibiotic susceptibility pattern of anaerobic organisms causing bloodstream infections in East Sussex Healthcare Trust, England and evaluate the efficacy of empirical antimicrobial therapy.

METHODS

We conducted a retrospective study on patients from the East Sussex area who were admitted in East Sussex Healthcare Trust with blood cultures diagnostic workup during July 2007 and June 2017. East Sussex Healthcare Trust is comprised of two acute hospitals (Eastbourne District General Hospital and The Conquest Hospital) with a total of 800 beds.

During the study period, attending physicians ordered a pair of blood culture on patients with bloodstream infections. A pair of blood culture consists of one aerobic and one anaerobic bottle. The blood cultures were collected by the medics, nursing staff or dedicated phlebotomy teams. Blood samples were added into blood culture bottles and loaded into an automated blood culture system (BacT/ALERT, Biomerieux, Durham, NC, USA) and incubated at 37 °C for five days. All bottles showing bacterial growth were subcultured on to agar (nutrient, chocolate) plates and incubated under both aerobic and anaerobic conditions (FAA or blood containing metronidazole 5 µg disc). Isolated anaerobic bacteria were identified by the conventional and automated method systems such as API, VITEK II (BioMeurex) and MALDI-TOF MS (Bruker Daltonik, Bremen, Germany).

Antibiotic susceptibility testing on anaerobic organisms was done by the disc diffusion method and the results were interpreted in accordance with EUCAST (The European Committee on Antimicrobial Susceptibility Testing) [10]. Antibiotic sensitivity was done by using clindamycin, amoxicillin/clavulanic acid, metronidazole, penicillin discs and E-test strips

were also used on Muller-Hinton agar plates where indicated to determine the antibiotic sensitivity on anaerobes (EUCAST).

Standards / guidelines / evidence base

The antibiotic guidelines at East Sussex Healthcare Trust for the management of sepsis in patient suggest amoxicillin/clavulanic acid and gentamicin as first line therapy. It is also recommended to take microbiology specimens for culture and sensitivity before initiation of antimicrobial therapy. Alternative therapies included piperacillin/tazobactam, or meropenem or metronidazole and either vancomycin and gentamicin or vancomycin and ciprofloxacin.

RESULTS

During the study period, 106,905 blood cultures were processed in the microbiology laboratory. A total of 324 anaerobic organisms were isolated from 312 blood cultures on 310 patients (167 males), representing a positivity rate of 0.30% of total blood cultures and 2.41% of positive blood cultures (13,425). Approximately 76% (238 episodes) of anaerobic bacteremia occurred in >60 years old (236) patients. Figure 1 illustrates the age distribution of all patients with anaerobic blood stream infections. The incidence of anaerobic BSI fluctuated every year during the study period by reaching up to 42 cases in 2010 and 2016 and hitting as low as 17 cases in 2014. Nineteen, 23, 35, 31, 20, 26, 32 and 25 cases were reported in 2007, 2008, 2009, 2011, 2012, 2013, 2015 and 2017, respectively.

The admitting services were: emergency department (ED) (40%, 125), medical (25%, 78), surgical (56, 16%) critical care unit (21, 7%), hematology (17, 5%), urology (8, 3%), and others (7, 3%).

Of 324 anaerobic organisms, the most frequent isolates were *Bacteroides spp.* (135, 42%), *Clostridium spp.* (79, 24%), and *Propionibacterium spp.* (28, 9%). Other 78 organisms included anaerobic Gram negative bacilli, *Fusobacterium spp.*, *Prevotella spp.*, anaerobic cocci, *Veillonella spp.*, and *Peptostreptococcus spp.* (Table 1). A total of 175 Gram negative bacilli were isolated. Of 175 Gram negative bacilli, *Bacteroides spp.* were predominant (135, 77%). Twenty-two Gram negative bacilli remained unidentified. Among

the spore forming organisms (79), *Clostridium perfringens* were the most commonly isolated organism. Polymicrobial anaerobic infections were recorded in 45 episodes and 60 aerobic organisms were isolated. Most commonly isolated organisms along with anaerobes were *Escherichia coli* (19), *Klebsiella spp.* (9), *Streptococcus spp.* (8), Coagulase negative *Staphylococcus* (6), *Enterococcus spp.* (5) and *Staphylococcus aureus* (3).

Antibiotic sensitivity

Metronidazole was highly effective against *Clostridium spp.* (99%), *Bacteroides spp.* (99%), *Fusobacterium spp.* (91%) and *Prevotella spp.* (100%). On the other hand, 99% *Clostridium spp.*, 92% *Bacteroides spp.*, 83% *Prevotella spp.* and 82% *Fusobacterium spp.* were sensitive to amoxicillin/clavulanic acid respectively. Antibiotic sensitivity rates of important causing blood stream infections are summarized in Table 2. Amoxicillin/clavulanic acid, metronidazole, clindamycin remained most effective antibiotics against anaerobes with a sensitivity rate of 93%, 92%, and 81% respectively. On the contrary penicillin was least sensitive (43%) against anaerobes (Figure 2).

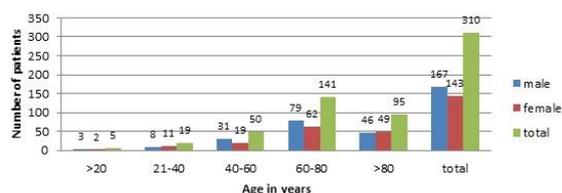


Figure 1. Age distribution of 310 patients with anaerobic bacteremia.

Table 1. Distribution of anaerobic *spp.* among the 312 anaerobic bacteremia episodes.

Organism	Total (%) n=324
Gram (-) bacilli	
All <i>Bacteroides</i>	135 (42)
<i>Bacteroides fragilis</i>	118 (36)
<i>Bacteroides spp.</i>	17 (5)
<i>Fusobacterium spp.</i>	11 (3)
<i>Prevotella spp.</i>	7 (2)
Others	22 (6)
Spore forming Gram (+) bacilli	
All <i>Clostridium</i>	79 (24)
<i>Clostridium perfringens</i>	35 (11)
<i>Clostridium septicum</i>	13 (4)
<i>Clostridium ramosum</i>	13 (4)
<i>Clostridium spp.</i>	18 (6)
Anaerobic cocci	
<i>Peptostreptococcus</i>	8 (2)
<i>Veillonella</i>	5 (2)
Other anaerobic cocci	23 (6)
Other Gram (+) bacilli	
<i>Propionibacterium</i>	28 (9)
<i>Actinomyces</i>	3 (1)
Others	3 (1)

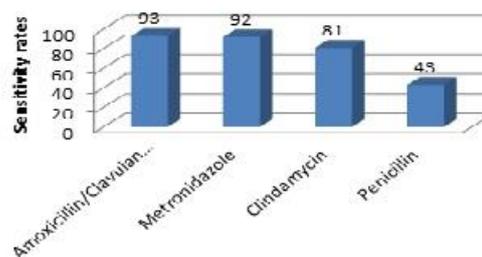


Figure 2. Antibiotic sensitivity rates in anaerobes causing blood stream infections.

Table 2. Antibiotic sensitivity profile of most common anaerobes from blood culture

Variables	Clindamycin, Sensitivity (%)	Amoxicillin/clavulanic acid Sensitivity (%)	Metronidazole Sensitivity (%)	Penicillin Sensitivity (%)
All <i>Bacteroides</i>	102/135 (75)	124/135 (92)	134/135 (99)	7/135 (5)
<i>Bacteroides fragilis</i>	89/118 (75)	108/118 (84)	116/117 (99)	2/118 (2)
<i>Bacteroides spp.</i>	13/18 (72)	16/17 (94)	18/18 (100)	5/17 (29)
All <i>Clostridium</i>	56/78 (72)	77/78 (99)	77/78 (99)	72/78 (92)
<i>Clostridium perfringens</i>	27/35 (77)	34/35 (97)	35/35 (100)	35/35 (100)
<i>Clostridium ramosum</i>	2/12 (17)	13/13 (100)	14/14 (100)	12/13 (92)
<i>Clostridium septicum</i>	13/13 (100)	13/13 (100)	13/14 (93)	13/13 (100)
<i>Clostridium spp.</i>	14/18 (78)	17/17 (100)	17/17 (100)	12/18 (67)
<i>Propionibacterium spp.</i>	5/7 (71)	24/24 (100)	4/26 (18)	26/26 (100)
<i>Fusobacterium spp.</i>	9/10 (90)	9/11 (82)	10/11 (91)	8/11 (73)
<i>Prevotella spp.</i>	5/7 (71)	5/6 (83)	7/7 (100)	2/6 (33)
<i>Veillonella spp.</i>	5/5 (100)	5/5 (100)	4/4 (100)	2/5 (40)
Other Gram (-) organisms	11/14 (79)	13/14 (93)	15/15 (100)	5/18 (28)

DISCUSSION

Anaerobic blood stream infections are rare in the hospitalized patients, however several risk factors such as recent abdominal surgery, cancer, intensive cancer therapy, bone marrow transplant, increased age, pre-existing heart, kidney and liver disease, have been identified for anaerobic bloodstream infections [5]. Studies around the world reported the significant decline in the occurrence of anaerobic blood stream infections [11,12]. The incidence of anaerobic bloodstream infections in this study was low (average 31/year). It accounted only 0.30% of all total blood cultures which is much lower than previous studies [1-3]. One study reported only 4% anaerobic bloodstream infections of all positive blood culture [13]. The anaerobic blood stream infections positive rate of all positive blood culture in this study was 2.4% which was lower than previous study [13]. There could be several reasons of low rate of anaerobic blood stream infections now a days such as routine bowel preparation before surgery, appropriate use of antibiotic prophylaxis and use of empirical antibiotics which are effective against anaerobes. In the past, use of anaerobic blood culture bottle was questioned in the literature. One study from Malaysia reported that facultative anaerobes and aerobes were more frequently isolated from the anaerobic bottle of blood culture set. The authors in this study recommended the use of aerobic-anaerobic pair of bottles rather than aerobic-aerobic pair of blood culture [14]. In our Trust, aerobic and anaerobic blood culture bottle are used for adults and only aerobic bottle for pediatric patients. Anaerobic blood stream infections are uncommon in children; however elderly population is at risk of this infection. In this study, 76% episode occurred in more than 60 years old patients. *Bacteroides spp.* accounted for 41% to all anaerobic blood stream infections; followed by *Clostridium spp.* and *Propionibacterium spp.*. Tan T et al [15] from Singapore described the similar prevalence of anaerobes from bloodstream infections. Bloodstream infections due to *Bacteroides spp.* and *Clostridium spp.* are usually considered as significant bacteremia. The mortality rates in *Bacteroides* and *Clostridium spp.* have been reported between 20-30% [16,17]. Other anaerobes such as *Fusobacterium spp.*,

Veillonella spp., *Prevotella spp.*, *Peptostreptococcus* and anaerobic cocci also cause significant bacteremia. On the contrary, *Propionibacterium* are usually considered as skin contaminant.

Antimicrobial susceptibility testing on the isolated anaerobes showed that metronidazole, amoxicillin/clavulanic acid (beta lactamase inhibitor) and clindamycin are effective against the isolated anaerobes. One study from Norway reported high sensitivity rates in anaerobes causing bloodstream infections to metronidazole, beta-lactam/beta-lactamase inhibitors and imipenem and reduced sensitivity to clindamycin and penicillin [18]. In our study, majority of the anaerobes were sensitive to beta-lactam/beta-lactamase inhibitors (amoxicillin/clavulanic acid) and metronidazole. So other beta-lactam/beta-lactamase inhibitor such as piperacillin/tazobactam or carbapenems and metronidazole can be effective. These antibiotics can be used as empirically where there is suspicion of anaerobic infection. Non-spore forming Gram positive rods such as *Propionibacterium spp.*, usually considered as a colonizer, are intrinsically resistant to metronidazole [19]. Metronidazole sensitivity rate excluding *Propionibacterium spp.* was much higher (99%). On the contrary penicillin was least effective (43%) against anaerobes (Table 2) and our findings are consistent with previous study [18]. This means that the empirical use of penicillin is not a good option. Appropriate antimicrobial therapy in anaerobic blood stream infections remains essential to achieve desirable outcome and increase the chances of survival.

This study highlights a low rate of anaerobic bacteremia during 10 years with *Bacteroides spp.* as the predominant organism. Most episodes occurred in elderly population which may be due to their co-morbidities. A total of 40% episodes occurred in ED, empirical agents active against anaerobes should be considered in patients presenting with bacteremia in ED. This study also confirms that the empirical antibiotic therapy used in our Trust remains appropriate as more than 92% isolates were sensitive to amoxicillin/clavulanic acid and metronidazole. We recommend periodic epidemiology and resistance surveillance in anaerobic bacteremia to guide empirical antibiotic therapy.

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