Washington University School of Medicine
Digital Commons@Becker

ICTS Faculty Publications | Institute of Clinical and Translational Sciences

2008

Gram-negative bacteraemia in non-ICU patients: factors associated with inadequate antibiotic therapy and impact on outcomes

Jonas Marschall
Washington University School of Medicine in St. Louis

Denis Agniel
Washington University School of Medicine in St. Louis

Victoria J. Fraser
Washington University School of Medicine in St. Louis

Joshua Doherty
Center for Healthcare Quality and Effectiveness, BJC Healthcare, St Louis

David K. Warren
Washington University School of Medicine in St. Louis

Follow this and additional works at: http://digitalcommons.wustl.edu/icts_facpubs

Part of the Medicine and Health Sciences Commons

1 **Gram-negative Bacteraemia in Non-ICU Patients: Factors Associated**

2 **with Inadequate Antibiotic Therapy and Impact on Outcomes**

3

4 Jonas Marschall, MD[1][*], Denis Agniel[1], Victoria J Fraser, MD[1], Joshua Doherty, BS[2],

5 David K Warren, MD, MPH[1]

6 [1] Division of Infectious Diseases, Washington University School of Medicine, St. Louis,

7 MO; [2] Center for Healthcare Quality and Effectiveness, BJC Healthcare, St. Louis, MO

8

9 **Running title**: Gram-negative bacteraemia outside the ICU

10

13

14 **Corresponding author and reprint requests to**:

15 Jonas Marschall, MD

16 Division of Infectious Diseases, Washington University School of Medicine, 660 S.

17 Euclid, St. Louis 63110, MO, USA

18 Phone: (001) 314 454-8044, Fax: (001) 314 454-8294, E-mail: jmarscha@im.wustl.edu

19

20

21 **Word count**:

22 Text: 2793   Synopsis: 235 (<250)   References: 41

23 Tables: 2   Figures: 1

24   **Synopsis**

25

26   **Background:** A considerable number of Gram-negative bacteraemias occur outside

27   intensive care units (ICUs). Inadequate antibiotic therapy in ICUs has been associated

28   with adverse outcomes; however, there are no prospective studies in non-ICU patients.

29   **Methods**: A 6-month (8/1/06-1/31/07), prospective cohort study of non-ICU patients

30   with Gram-negative bacteraemia in a tertiary care hospital was performed. Inadequate

31   empirical antibiotic therapy was defined as no antibiotic or starting a non-susceptible

32   antibiotic within 24 hours after the initial positive blood culture.

33   **Results**: 250 non-ICU patients had Gram-negative bacteraemia. Mean age=56.4 ($\pm$16.1)

34   years. The predominant bacteria in monomicrobial infections were *E. coli* (24%), *K.*

35   *pneumoniae* (18%), and *P. aeruginosa* (8%). Sixty-one (24%) patients had polymicrobial

36   bacteraemia. Seventy patients (28%) required ICU transfer, and 35 (14%) died.

37   Seventy-nine (31.6%) received inadequate empirical antibiotic therapy. These patients

38   were more likely to have a hospital-acquired infection [Odds ratio (OR)=1.99, 95%

39   confidence interval (CI)=1.11-3.56, p=0.02] and less likely to have *E. coli*

40   monomicrobial bacteraemia [OR=0.40 (95% CI 0.19-0.86), p=0.02]. There were no

41   differences in occurrence of sepsis [72 (91.1%) patients with inadequate vs. 159 (93.0%)

42   with adequate therapy; p=0.6], ICU transfer [20 (25.3%) vs. 50 (29.2%); p=0.5], post-

43   bacteraemia length of stay (median=6.8 vs. 6.1 days; p=0.09) or death [11 (13.9%) vs. 24

44   (14.0%); p=1.0].

45   **Conclusions**: <mark>Nearly</mark> one-third of non-ICU patients with Gram-negative bacteraemia

46   received inadequate empirical antibiotic therapy. There was no difference in adverse

47   outcomes between patients receiving inadequate or adequate therapy in this study.

48

Introduction

Approximately 250,000 episodes of bloodstream infections occur in the United States annually.[1] Bloodstream infections have an overall mortality rate of 18%, making them one of the leading causes of death in the U.S.[2] Over the last two decades, Gram-negative bacteria have become a less frequent cause of bloodstream infections,[3] since the increased use of indwelling vascular devices has resulted in a larger proportion of Gram-positive bacteraemias.[1] However, there is evidence that Gram-negative bacteraemias are increasing once again.[4] Antibiotic resistance among Gram-negative bacteria is also increasing.[5] There has been limited development of new antibiotics with Gram-negative activity,[6,7] which has made the treatment of Gram-negative bacteraemia more difficult.

Previous studies of bloodstream infections have focused primarily on ICU-acquired infections, because critically ill patients represent a well-defined and highly vulnerable population.[8,9] However, bloodstream infections among hospitalized patients outside the ICU account for at least half of all nosocomial bloodstream infections.[10] These infections in non-ICU patients have rarely been investigated separately.[11,12] This is presumably because they were believed to be associated with less morbidity and mortality than in ICU patients, and also because the distribution of non-ICU patients in a hospital requires more workforce to conduct a prospective study. Little data are available on the demographic characteristics of non-ICU patients with Gram-negative bacteraemia, and their clinical outcomes.

Several studies have demonstrated that inadequate empirical antibiotic treatment of bacteraemia is associated with poor outcome.[13–16] These studies have mainly focused

72   on ICU patients or have been carried out in diverse populations.[17] Inadequate empirical

73   treatment was reported in 23-30% of cases in previous studies. However, a 53% rate of

74   inadequate treatment was reported in infections due to antibiotic-resistant organisms.[18] If

75   similar rates of inadequate treatment exist in non-ICU patients, empirical antibiotic

76   prescribing practices would need to be re-examined.

77   In this study, we describe the epidemiology of Gram-negative bacteraemia in non-

78   ICU patients at a tertiary-care hospital, investigate the frequency of inadequate antibiotic

79   treatment, elicit predisposing factors for inadequate therapy, and determine its impact on

80   clinical outcomes.

81

82   **Patients and Methods**

83

84   *Setting*

85   Barnes-Jewish Hospital (BJH), a 1250-bed teaching hospital, is the largest hospital in

86   Missouri, with a referral base that includes the Saint Louis metropolitan area, eastern

87   Missouri and western Illinois.

88

89   *Study design*

90   We performed a prospective cohort study of patients with Gram-negative bacteraemia

91   during a 6-month period from August 1st, 2006 until January 31st, 2007. An automated

92   query of all non-ICU patients with a blood culture growing ≥ 1 species of Gram-negative

93   bacilli was performed using electronic data from a BJC Healthcare clinical data

94   repository and the results were sent daily to one of the investigators (J.M.).

95

96   *Inclusion and exclusion criteria*

97   All adult patients admitted to non-ICU wards who presented with or developed Gram-

98   negative bacteraemia (≥ 1 positive blood culture) were included. Polymicrobial infections

99   were also included if at least one Gram-negative organism was present. Subsequent

100   episodes of bacteraemia in study patients were excluded from the analysis. Patients who

101   were bacteraemic as an outpatient (in clinics or in the emergency department) and who

102   were discharged to home before the results of the culture were known were excluded. We

103   also excluded patients who were initially identified as having a Gram-negative

104   bacteraemia, but were determined to have Gram-positive organisms in the final

105   laboratory identification (n=4).

106

107   *Data collection*

108   Paper and electronic medical records of patients who met inclusion criteria were

109   reviewed for demographics, medical history, home medication, and possible sources of

110   infection. Information on all positive clinical cultures other than blood cultures was also

111   collected to determine any potential focus of infection. Charlson comorbidity[19] and

112   McCabe severity of illness[20] scores were computed for each patient. Patients' vital signs,

113   laboratory, pharmacy, and radiological data were continuously reviewed during the

114   admission. Medication information was entered sequentially as start and stop date and

115   time for each antibiotic.

116   Key clinical outcomes measured included the development of hypotension, multiple

117   organ dysfunction syndrome, ARDS, mechanical ventilation, any subsequent transfer to

118   the ICU, length of hospital stay after detection of positive blood cultures, and in-hospital

119   mortality.

120

121   *Definitions*

122   Adequacy of antibiotic therapy was determined at various time periods: 1) within 24

123   hours of the time the blood culture was drawn, 2) within 24 hours of notification of

124   bacterial growth (which coincided with the notification of Gram stain results), 3) within

125   24 hours of bacterial identification, and 4) within 24, 48, and 72 hours of notification of

126   antibiotic susceptibility results. Inadequacy of antibiotic treatment was defined as no

127 antibiotic or no susceptibility-matching antibiotic administered during each of these time

128 periods in order to reflect the dynamics of inadequate treatment. Various time periods

129 have been examined in the literature, including antibiotic treatment during a period of 24

130 hours from time of blood culture sampling,[18,21,14,13,22] at the time when antibiotic

131 susceptibility results are available,[23,15] or during 48 hours from the time of notification of

132 susceptibilities.[17] We analyzed inadequate treatment within 24 hours of blood culture

133 sampling, since this definition has been used in the largest number of studies. If antibiotic

134 susceptibility testing was not performed, we decided on a case-by-case basis whether

135 treatment could be considered adequate, based on the antibiogram for that particular

136 organism at Barnes-Jewish Hospital. Multi-drug resistance was defined using previously

137 published criteria.[24]

138 Sepsis, sepsis-induced hypotension, and multiple organ dysfunction syndrome were

139 defined using established criteria.[25] A bacteraemia was classified as community-acquired

140 if the first positive blood culture occurred ≤48 hours after hospital admission.[26]

141 Neutropenia was defined as white blood cell count <1.0 G/L. Medical

142 immunosuppression was defined as receipt of prednisone equivalent of ≥10mg daily or

143 any other immunosuppressant (e.g., cyclosporine, methotrexate, etc.) during the 30 days

144 prior to admission.

145

146 *Microbiological methods*

147 Work-up of all blood cultures was performed by the BJH Clinical Microbiology

148 Laboratory. Blood cultures were incubated in the Bactec 9240 system (Becton-Dickinson

149   Diagnostic Systems, Sparks, MD). Standard microbiological methods for identification

150   and antibiotic susceptibility testing were employed.[27]

151   In our institution, the microbiology laboratory notifies the clinician when a blood culture

152   becomes positive. Following notification, the clinician is responsible for reviewing

153   subsequent bacterial identification and antimicrobial susceptibility results in the hospital

154   computer system.

155

156   *Data analysis and statistical methods*

157   Data entry was performed using Microsoft Access and Excel (Microsoft Corp., Redmond,

158   WA), and data analysis was performed using SPSS 14 (SPSS Inc., Chicago, IL).

159   Univariate comparisons among categorical variables were performed using the χ^2

160   test or Fisher's exact test as appropriate. Comparisons among continuous independent

161   variables were performed using Student's t test or Mann Whitney U test as appropriate. A

162   two-sided p value of <0.05 was considered significant. Variables found to have a $p<0.1$

163   on univariate testing were considered for entry into a forward stepwise multivariate

164   logistic regression model. The study was approved by the Washington University Human

165   Research Protection Office (No. 06-0638). Due to the observational design of the study

166   informed consent was not required.

167

168   **Results**

169

170   ***The epidemiology of Gram-negative bacteraemia outside the ICU***

171   Two hundred and ninety-four patients had a Gram-negative bacteraemia during the study

172   period. Of these, 44 (15.0%) patients were ICU patients, leaving 250 patients for analysis

173   (Table 1).

174   There were 160 (64.0%) community-acquired and 90 (36.0%) hospital-acquired

175   infections. The predominant organisms in monomicrobial bacteraemias were *E. coli*

176   (n=59; 24%), *K. pneumoniae* (45; 18%), and *P. aeruginosa* (19; 8%). Sixty-one

177   bacteraemias were polymicrobial (24.4%) (Table 2). There were 12 (4.8%) multi-drug

178   resistant organisms among the isolates.

179   Two hundred and thirty-one (92.4%) patients were septic at the time of blood culture, 105

180   (42.0%) developed hypotension, and 11 (4.4%) multiple organ dysfunction syndrome.

181   Transfer to ICU was necessary in 70 (28.0%) patients. In-hospital mortality was 14.0%

182   (n=35).

183

184   ***The frequency of inadequate antibiotic treatment of Gram-negative bacteraemia***

185   The antibiotics with Gram-negative activity that were most frequently prescribed during

186   the 24-hour period after the initial positive blood culture was drawn were cefepime (109;

187   in 43.6% of episodes), ciprofloxacin (57; 22.8%), piperacillin/tazobactam (39; 15.6%),

188   gentamicin (28; 11.2%), ceftriaxone (22; 8.8%), meropenem (9; 3.6%), and

189   ampicillin/sulbactam (5; 2.0%). In 57 cases (22.8%) more than one antibiotic was given

190   in this time period.

191 Seventy-nine (31.6%) patients received inadequate empirical antibiotic treatment. In 38

192 (48.1%) of cases inadequate treatment was due to failure to administer antibiotics with

193 Gram-negative coverage within 24 hours of the initial positive blood culture, and in 41

194 (51.9%) cases was due to a Gram-negative bacillus that was resistant to the prescribed

195 antibiotic. Within 24 hours after notification of antibiotic susceptibilities, 28 of 197

196 patients (14.2%) were still receiving inadequate antibiotic treatment (Figure 1).

197

198 *Factors associated with inadequate empirical antibiotic treatment of Gram-negative*

199 *bacteraemia*

200 Among patients receiving inadequate versus adequate empirical treatment within the first

201 24 hours after the initial blood culture was drawn, there were no significant differences in

202 mean age [55.3 years (±17.0) vs. 56.9 years (±15.8), p=0.5], male gender [43 (54.4%) vs.

203 83 (48.5%), p=0.4], body mass index (median 25.3 vs. 27.3, p=0.12), Charlson score

204 (median 3 vs. 4, p=0.4), McCabe score (median 1 vs. 1, p=0.2) (Table 1), or in type of

205 service admitting the patient (data not shown). Patients with hospital-acquired

206 bacteraemia were more often inadequately treated than those with community-acquired

207 bacteraemia [37 (46.8%) vs. 53 (31.0%) patients, p=0.02].

208 *E. coli* was less likely to be the cause of inadequately treated bacteraemia [10

209 (12.7%) vs. 49 (28.7%), p=0.006]. Apart from resistance to ampicillin (58% of

210 monomicrobial *E. coli* bacteraemias), *E. coli* were most often resistant to

211 trimethoprim/sulfamethoxazole (21; 35.6%), ciprofloxacin (18; 30.5%), gentamicin (7;

212 11.9%), and piperacillin/tazobactam (2; 3.4%). Treatment was less often inadequate if the

213 bloodstream infection had a urinary tract source, [14 (20.9%) urinary vs. 65 (35.5%) non-

214 urinary source, p=0.03].

215   In multivariate analysis, hospital-acquired bacteraemia [OR 1.99 (95% CI 1.11-

216 3.56), p=0.02] was associated with receiving inadequate empirical antibiotic treatment.

217 Mucositis at time of blood culture [OR 0.23 (95% CI 0.06-0.84), p=0.03], and presence

218 of *E. coli* monomicrobial bacteraemia [OR 0.40 (95% CI 0.19-0.86), p=0.02] were more

219 commonly associated with adequate antibiotic use (Table 1).

220

221 ***The outcome of inadequately empirically treated Gram-negative bacteraemia***

222 Comparing the outcomes of inadequately versus adequately treated infections, there were

223 no differences in transfer to the ICU [20 (25.3%) vs. 50 (29.2%), p=0.5], length of

224 hospital stay after positive blood culture [median 6.8 days (range 1-89) vs. 6.1 days (1-

225 106), p=0.09], or in-hospital mortality [11 (13.9%) vs. 24 (14.0%), p=1.0]. When

226 adjusting the effect of inadequate treatment for the Charlson comorbidity score, previous

227 exposure to steroids, and neutropenia (all of which had been found to be associated with

228 mortality in univariate analysis), inadequate treatment did not remain in the final model

229 (data not shown). There was no difference in mortality whether cefepime had been used

230 for empirical treatment or not [17 (15.6%) patients exposed to cefepime vs. 18 (12.8%)

231 not exposed; p=0.5].

232   Definitive treatment (defined as administration of an antibiotic that matched the

233 bacteria's susceptibility pattern within 24 hours of notification of susceptibilities) was

234 more often inadequate if empirical antibiotic treatment had been inadequate compared to

235   if it had been adequate [20 (30.8%) with inadequate empirical therapy vs. 8 (6.1%) with

236   adequate empirical therapy, p<0.001].

237

Discussion

Non-ICU patients account for approximately half of the bloodstream infections in the hospital.[2,10] An even larger proportion of Gram-negative bacteraemias (62-95%) occurs in non-ICU patients.[28–30] Nevertheless, bacteraemias have rarely been investigated outside the intensive care unit,[11,12,31] which may be due to the heterogeneity of non-ICU patients. To our knowledge, this is the first prospective study of Gram-negative bacteraemia in the non-ICU hospitalized population. During the study period, non-ICU patients accounted for 85% (250 of 294) of all Gram-negative bacteraemias in this hospital. The demographics, comorbidities, and microbiology of infections in this study are similar to retrospective studies of Gram-negative bacteraemias in hospitalized patients.[28,29,32,33] Urinary tract infections were the predominant source of bacteraemia and *E. coli* was the most frequently detected organism. This is in contrast to Gram-negative bacteraemias in ICU patients, which frequently originate from the respiratory[34] or gastrointestinal tract[35] and are more often caused by *P. aeruginosa*.[31]

Twenty-eight percent of patients were transferred to the ICU after the bacteraemia had occurred. The in-hospital mortality was substantial (14%), but less than the 24% mortality rate in a Danish population-based study,[28] or in studies of ICU patients with Gram-negative bacteraemia (49-60%).[34,35] This is likely due to differences in population characteristics including different levels of severity of underlying illnesses, but might also point to differences in the management of sepsis rather than antibiotic treatment.

260   One of the major modifiable factors influencing the outcome of bacteraemia is the

261   adequacy of antibiotic treatment.[36] This was demonstrated in studies including ICU

262   patients.[13-17,23] However, no study has examined the effect of adequate antibiotic

263   treatment on outcomes in non-ICU patients only. We demonstrated rates of inadequate

264   empirical treatment during the first 24 hours after the blood culture (31.6%) similar to the

265   30% - 37% reported from other prospective studies.[15,17] In approximately half of the

266   cases, inadequate treatment was due to failure to administer an antibiotic with Gram-

267   negative activity.

268   Hospital-acquired bacteraemia was a risk factor for receiving inadequate

269   empirical antibiotic treatment in our cohort. This has been noted previously,[22,21,13-15] and

270   suggests that physicians are often unaware of the different microbiological patterns in the

271   hospital versus the community. Increasing antibiotic resistance and lack of prescriber

272   knowledge regarding appropriate antibiotics for likely in-hospital pathogens may lead to

273   the institution of inadequate empirical antibiotic treatment. Decision support tools, based

274   on local bacterial antimicrobial resistance patterns in association with clinical information

275   and inclusion of Gram stain results, may improve the choice of empirical therapy.[37,38]

276   Several other risk factors for inadequate treatment have been found, e.g. previous

277   antibiotic treatment,[14,13] hospital admission in the 90 days prior to the current

278   admission,[21] polymicrobial infections,[14] and *Pseudomonas* infections,[22] which we did not

279   find. Conversely, *E. coli* infection was associated with less risk of inadequate treatment,

280   which has been reported before by others.[22,13] *E. coli* is the most frequent cause of Gram-

281   negative bacteraemia and is not as prone to multi-drug resistance as other Gram-negative

282   bacteria,[33] which may explain why it is generally better covered by empirical

antimicrobials. The finding that mucositis was protective against inadequate treatment might be related to mucositis being more often present in a subset of oncology patients, and a tendency to start broad-spectrum antibiotics with Gram-negative activity earlier in this population.

In our cohort of patients, inadequate empirical treatment was not associated with deterioration of status (transfer to ICU, length of hospital stay, or increased in-hospital mortality). This is in contrast to many studies, in which inadequate treatment was associated with adverse outcomes.[13-17,23] However, a few studies that included mixed ICU and non-ICU patient populations have not found this association.[22,21] One possible explanation for our finding is that non-ICU patients in general have a lower severity of illness compared to ICU patients and therefore, the role of the adequate antibiotic treatment may be less crucial.[36] A study underlining this assumption showed that inadequate treatment was more frequently administered in less severely ill patients, with no discernable impact on outcomes.[22] Interventions focused on optimizing treatment for non-ICU patients would likely have the greatest benefit in e.g., neutropenic patients, transplant patients, and patients at risk for *Pseudomonas* bacteraemia.

In addition, we did not find that the use of cefepime for empirical treatment was associated with increased all-cause mortality as a recent meta-analysis has reported.[39]

There are some limitations to our study. First, this is a single, tertiary care hospital and may reflect process issues unique to this facility. In our hospital the clinician is only directly notified by the microbiology laboratory when a blood culture turns positive, but

306   needs to look up subsequent bacterial identification and antimicrobial susceptibility

307   results in the hospital computer system. This may cause delays in starting adequate

308   antibiotic treatment. We also only collected crude mortality, not attributable mortality.

309   The sample size is large for a single-center prospective study but may still be small to

310   detect a difference in outcomes, like Fraser and colleagues reported from a mixed ICU

311   and non-ICU population.[40]

312   One of the strengths of this prospective study is the detailed sequential analysis of

313   the adequacy of antibiotic treatment at different time points. Previous studies of the

314   adequacy of treatment have analyzed one specific time frame and not taken into account

315   the dynamic that is inherent in the processing of blood cultures and the notification of

316   results to the treating physician. We also evaluated empirical and definitive therapy

317   separately, and controlled for baseline severity of illness.[41] At our institution, antibiotic

318   treatment is initiated by clinicians from various specialties and levels of professional

319   experience and is therefore diverse, which adds to the generalizability of our findings.

320

321   Our study is the first to prospectively describe the epidemiology of Gram-

322   negative bacteraemias in non-ICU patients. The frequency of inadequate empirical

323   antibiotic treatment is similar to data from ICUs. The administration of inadequate

324   treatment did not confer worse patient outcomes. Therefore, while adequate antibiotic

325   therapy is an important factor, our findings suggest that there are other factors that may

326   be more important in determining the prognosis in the non-ICU population.

327

345   **References**

346

347   1. Pittet D, Wenzel RP. Nosocomial bloodstream infections. Secular trends in rates,

348   mortality, and contribution to total hospital deaths. *Arch Intern Med* 1995; **155**:

349   1177-84.

350   2. Weinstein MP, Towns ML, Quartey SM *et al*. The clinical significance of positive

351   blood cultures in the 1990s: a prospective comprehensive evaluation of the

352   microbiology, epidemiology, and outcome of bacteremia and fungemia in adults.

353   *Clin Infect Dis* 1997; **24**: 584-602.

354   3. Gaynes R, Edwards JR, and the National Nosocomial Infections Surveillance

355   System. Overview of nosocomial infections caused by Gram-negative bacilli. *Clin*

356   *Infect Dis* 2005; **41**: 848-54.

357   4. Albrecht SJ, Fishman NO, Kitchen J *et al*. Reemergence of gram-negative health

358   care-associated bloodstream infections. *Arch Intern Med* 2006; **166**: 1289-94.

359   5. D'Agata EM. Rapidly rising prevalence of nosocomial multidrug-resistant, Gram-

360   negative bacilli: a 9-year surveillance study. *Infect Control Hosp Epidemiol* 2004;

361   **25**: 842-6.

362   6. Li J, Nation RL, Turnidge JD *et al*. Colistin: the re-emerging antibiotic for

363   multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6**:

364   589-601.

365   7. Rice LB. Challenges in identifying new antimicrobial agents effective for treating

366   infections with *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin*

367   *Infect Dis* 2006; **43** Suppl 2: S100-5.

368   8. Warren DK, Zack JE, Elward AM *et al*. Nosocomial primary bloodstream

369   infections in intensive care unit patients in a nonteaching community medical

370   center: A 21-month prospective study. *Clin Infect Dis* 2001; **33**: 1329-35.

371   9. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill

372   patients. Excess length of stay, extra costs, and attributable mortality. *JAMA*

373   1994; **271**: 1598-601.

374   10. Edmond MB, Wallace SE, McClish DK *et al*. Nosocomial bloodstream infections

375   in United States hospitals: A three-year analysis. *Clin Infect Dis* 1999; **29**: 239-44.

376   11. Suljagic V, Cobeljic M, Jankovic S *et al*. Nosocomial bloodstream infections in

377   ICU and non-ICU patients. *Am J Infect Control* 2005; **33**: 333-40.

378   12. Garrouste-Orgeas M, Chevret S, Mainardi JL *et al*. A one-year prospective study

379   of nosocomial bacteraemia in ICU and non-ICU patients and its impact on patient

380   outcome. *J Hosp Infect* 2000; **44**: 206-13.

381   13. Bouza E, Sousa D, Munoz P *et al*. Bloodstream infections: A trial of the impact of

382   different methods of reporting positive blood culture results. *Clin Infect Dis* 2004;

383   **39**: 1161-9.

384   14. Harbarth S, Garbino J, Pugin J *et al*. Inappropriate initial antimicrobial therapy

385   and its effect on survival in a clinical trial of immunomodulating therapy for

386   severe sepsis. *Am J Med* 2003; **115**: 529-35.

387   15. Ibrahim EH, Sherman G, Ward S *et al*. The influence of inadequate antimicrobial

388   treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*

389   2000; **118**: 146-55.

390 16. Kollef MH, Sherman G, Ward S *et al*. Inadequate antimicrobial treatment of

391   infections. *Chest* 1999; **115**: 462-74.

392 17. Leibovici L, Shraga I, Drucker M *et al*. The benefit of appropriate empirical

393   antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;

394   **244**: 379-86.

395 18. Kang CI, Kim SH, Park WB *et al*. Bloodstream infections caused by antibiotic-

396   resistant Gram-negative bacilli; risk factors for mortality and impact of

397   inappropriate antimicrobial therapy on outcome. *Antimicrob Agents Chemother*

398   2005; **49**: 760-6.

399 19. Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic

400   comorbidity in longitudinal studies: Development and validation. *J Chron Dis*

401   1987; **40**: 373-83.

402 20. McCabe WR, Jackson GG. Gram-negative bacteremia. *Arch Intern Med* 1962;

403   **110**: 847-55.

404 21. McDonald JR, Friedman ND, Stout JE *et al*. Risk factors for ineffective therapy in

405   patients with bloodstream infection. *Arch Intern Med* 2005; **165**: 308-313.

406 22. Scarsi KK, Feinglass JM, Scheetz MH *et al*. Impact of inactive empiric

407   antimicrobial therapy on inpatient mortality and length of stay. *Antimicrob Agents*

408   *Chemother* 2006; **50**: 3355-60.

409 23. Micek ST, Lloyd AE, Ritchie DJ *et al*. *Pseudomonas aeruginosa* bloodstream

410   infection: importance of appropriate initial antimicrobial treatment. *Antimicrob*

411   *Agents Chemother* 2005; **49**: 1306-11.

412   24. Lockhart SR, Abramson MA, Beekmann SE *et al*. Antimicrobial resistance

413   among Gram-negative bacilli causing infections in intensive care unit patients in

414   the United States between 1993 and 2004. *J Clin Microbiol* 2007; **45**: 3352-9.

415   25. Bone RC, Balk RA, Cerra FB *et al*. Definitions for sepsis and organ failure and

416   guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM

417   Consensus Conference Committee. American College of Chest

418   Physicians/Society of Critical Care Medicine. *Chest* 1992; **101**: 1644-55.

419   26. Diekema DJ, Beekmann SE, Chapin KC *et al*. Epidemiology and outcome of

420   nosocomial and community-onset bloodstream infection. *J Clin Microbiol* 2003;

421   **41**: 3655-60.

422   27. Clinical and Laboratory Standards Institute. *Performance Standards for*

423   *Antimicrobial Susceptibility Testing: Sixteenth Informational Supplement, M100-*

424   *S16.* CLSI, Wayne, PA, USA, 2006.

425   28. Pedersen G, Schonheyder HC, Sorensen HT. Antibiotic therapy and outcome of

426   monomicrobial Gram-negative bacteraemia: a 3 year population based study.

427   *Scand J Infect Dis* 1997; **29**: 601-6.

428   29. Uzun O, Akalin HE, Hayran M *et al*. Factors influencing prognosis in bacteremia

429   due to Gram-negative organisms: evaluation of 448 episodes in a Turkish

430   university hospital. *Clin Infect Dis* 1992; **15**: 866-73.

431   30. Pittet D, Li N, Woolson RF *et al*. Microbiological factors influencing the outcome

432   of nosocomial bloodstream infections: a 6-year validated, population-based

433   model. *Clin Infect Dis* 1997; **24**: 1068-78.

434   31. Arvanitidou M, Katikaridou E, Douboyas J *et al*. Epidemiological characteristics

435   of nosocomial bacteraemias among ICU and non-ICU patients in a tertiary-care

436   hospital in Greece. *J Hosp Infect* 2005; **59**: 70-72.

437   32. Harbarth S, Rohner P, Auckenthaler R *et al*. Impact and pattern of Gram-negative

438   bacteraemia during 6y at a large university hospital. *Scand J Infect Dis* 1999; **31**:

439   163-8.

440   33. Diekema DJ, Pfaller MA, Jones RN *et al*. Survey of bloodstream infections due to

441   Gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of

442   isolates collected in the United States, Canada and Latin America for the

443   SENTRY Antimicrobial Surveillance Program, 1997. *Clin Infect Dis* 1999; **29**:

444   595-607.

445   34. Sligl W, Taylor G, Brindley PG. Five years of nosocomial Gram-negative

446   bacteremia in a general intensive care unit: epidemiology, antimicrobial

447   susceptibility patterns, and outcomes. *Int J Infect Dis* 2006; **10**: 320-5.

448   35. Gardiner DF, Scholand SJ, Babinchak T. Mortality and gram-negative rod

449   bacteraemia in the intensive care unit. *J Hosp Infect* 2006; **62**: 453-7.

450   36. Harbarth S, Nobre V, Pittet D. Does antibiotic selection impact patient outcome?

451   *Clin Infect Dis* 2007; **44**: 87-93.

452   37. Mullett CJ, Thomas JG, Smith CL *et al*. Computerized antimicrobial decision

453   support: an offline evaluation of a database-driven empiric antimicrobial guidance

454   program in hospitalized patients with a bloodstream infection. *Int J Med Inform*

455   2004; **73**: 455-60.

456   38. Hautala T, Syrjälä H, Lehtinen V *et al*. Blood culture Gram stain and clinical

457   categorization based empirical antimicrobial therapy of bloodstream infection. *Int*

458   *J Antimicrob Agents* 2005; **25**: 329-33.

459   39. Yahav D, Paul M, Fraser A *et al*. Efficacy and safety of cefepime: a systematic

460   review and meta-analysis. *Lancet Infect Dis* 2007; **7**: 338-48.

461   40. Fraser A, Paul M, Almanasreh N *et al*. Benefit of appropriate empirical antibiotic

462   treatment: Thirty-day mortality and duration of hospital stay. *Am J Med* 2006;

463   **119**: 970-6.

464   41. McGregor JC, Rich SE, Harris AD *et al*. A systematic review of the methods used

465   to assess the association between appropriate antibiotic therapy and mortality in

466   bacteremic patients. *Clin Infect Dis* 2007; **45**: 329-37.

Table 1. Comparison of 250 non-ICU patients receiving inadequate versus adequate empirical antibiotic treatment for Gram-

negative bacteraemia

	Total	Univariate analysis			Multivariate analysis
	n (%) (n=250)	Inadequate treatment (n=79)	Adequate treatment (n=171)	p value	Odds Ratio (95% CI)
Age, mean (± standard deviation), years	56.4 (±16.1)	55.3 years (±17.0)	56.9 years (±15.8)	0.5	-
Male gender	126 (50.4%)	43 (54.4%)	83 (48.5%)	0.4	-
Race					
- White	153 (61.2%)				
- African-American	94 (37.6%)				
- Other	3 (1.2%)				
LTCF resident	33 (13.2%)	12 (15.2%)	21 (12.3%)	0.5	-
Admitted within 3 months	146 (58.4%)	46 (58.2%)	100 (58.5%)	1.0	-
BMI (median, range), kg/m^2	26.4 (13.3-70.4)	25.3 (17.0-70.4)	27.3 (13.3-66.4)	0.12	-
Charlson comorbidity score (median, range)	4 (0-16)	3 (0-16)	4 (0-15)	0.4	-
McCabe severity of illness score (median, range)	1 (1-3)	1 (1-3)	1 (1-3)	0.2	-
Congestive heart failure	30 (12.0%)	6 (7.6%)	24 (14.0%)	0.15	-
Chronic pulmonary disease	44 (17.6%)	15 (19.0%)	29 (17.0%)	0.7	-
Malignancy	112 (44.8%)	31 (39.2%)	81 (47.4%)	0.2	-
- Leukaemia	27 (10.8%)	5 (6.3%)	22 (12.9%)	0.12	-

- Metastatic solid tumor	34 (13.6%)	10 (12.7%)	24 (14.0%)	0.8	-
- Neutropenia	36 (14.4%)	8 (10.1%)	28 (16.4%)	0.2	-
- Chemotherapy ≤30 days prior to admission	31 (12.4%)				
Received steroids ≤30 days prior to admission	35 (14.0%)				
Other immunosuppressive therapy	30 (12.0%)				
History of solid organ transplant	10 (4.0%)				
Bone marrow transplant (this admission)	10 (4.0%)				
Diabetes mellitus	87 (34.8%)	22 (27.8%)	65 (38.0%)	0.12	-
Hyperglycemia (>200 mg/dL)	41 (16.4%)	8 (10.1%)	33 (19.3%)	0.07	-
Renal insufficiency (Cr >1.5 mg/dL)	68 (27.2%)	25 (31.6%)	43 (25.1%)	0.3	-
Cerebrovascular disease	28 (11.2%)	7 (8.9%)	21 (12.3%)	0.4	-
Hemiplegia	15 (6.0%)	8 (10.1%)	7 (4.1%)	0.06	-
Liver disease	26 (10.4%)	12 (15.2%)	14 (8.2%)	0.09	-
Mucositis at time of blood culture	21 (8.4%)	3 (3.8%)	18 (10.5%)	0.08	0.23 (0.06-0.84)
Source of bloodstream infection					
- Urinary tract	67 (26.8%)	14 (17.7%)	53 (31.0%)	0.03	-
- Intravascular catheter	40 (16.0%)	18 (22.8%)	22 (12.9%)	0.047	-
- GI tract	41 (16.4%)				
- Respiratory tract	9 (3.6%)				
- Other source	28 (11.2%)				
- No source identified	65 (26.0%)				
Hospital-acquired bacteraemia	90 (36%)	37 (46.8%)	53 (31.0%)	0.02	1.99 (1.11-3.56)
E. coli, monomicrobial infection	59 (23.6%)	10 (12.7%)	49 (28.7%)	0.006	0.40 (0.19-0.86)
K. pneumoniae, monomicrobial infection	45 (18.0%)	11 (13.9%)	34 (19.9%)	0.3	-

P. aeruginosa, monomicrobial infection	19 (7.6%)	7 (8.9%)	12 (7.0%)	0.6	-
Polymicrobial infection	61 (24.4%)	24 (30.4%)	37 (21.6%)	0.14	-
Sepsis	231 (92.4%)	72 (91.1%)	159 (93.0%)	0.6	-
Sepsis-induced hypotension	105 (42.0%)	32 (40.5%)	73 (42.7%)	0.7	-
Outcomes					
- Multiple organ dysfunction syndrome	11 (4.4%)				
- Transfer to intensive care unit (ICU)	70 (28.0%)	20 (25.3%)	50 (29.2%)	0.5	-
- Mechanical ventilation after bacteraemia	29 (11.6%)				
- ARDS	6 (2.4%)				
- In-hospital mortality	35 (14.0%)	11 (13.9%)	24 (14.0%)	1.0	-

469

NOTE. LTCF = Long-term care facility. BMI = Body mass index. GI tract = Gastrointestinal tract. ARDS = Acute respiratory distress syndrome. Variables considered for entry in a forward stepwise multivariate logistic regression model included Hospital-acquired infection; Source, urinary tract; Source, intravascular catheter; Hemiplegia; *E. coli,* monomicrobial infection; Hyperglycemia; Mucositis; Liver disease. The -2 log likelihood value for the final model was 293.796, and the Hosmer-Lemeshow goodness-of-fit chi square test was 0.861 (p=0.835).

475

476 **Table 2. Bacterial isolates in 250 non-ICU patients with Gram-negative bacteraemia**

| Microorganism	n (%) n=274
Escherichia coli	77 (28%)
Klebsiella pneumoniae	67 (24%)
Pseudomonas aeruginosa	30 (11%)
Enterobacter cloacae	15 (5%)
Proteus mirabilis	13 (5%)
Acinetobacter baumannii	13 (5%)
Klebsiella oxytoca	8 (3%)
Stenotrophomonas maltophilia	6 (2%)
Other Gram-negative microorganisms	45 (16%)

477

478 NOTE. Sixty-one (24.4%) of 250 Gram-negative bacteraemia episodes were polymicrobial infections. The most frequent among the

479 45 other Gram-negative organisms were *Enterobacter aerogenes* (4), *Achromobacter* spp. (3), *Acinetobacter* spp. (3), *Citrobacter*

480 *freundii* (3), *Citrobacter koseri* (3), *Providencia* spp. (3), *Pseudomonas* spp. (3), and *Salmonella* spp. (3).

481 **Figure 1. Inadequate antibiotic treatment among non-ICU patients with Gram-negative bacteraemia**
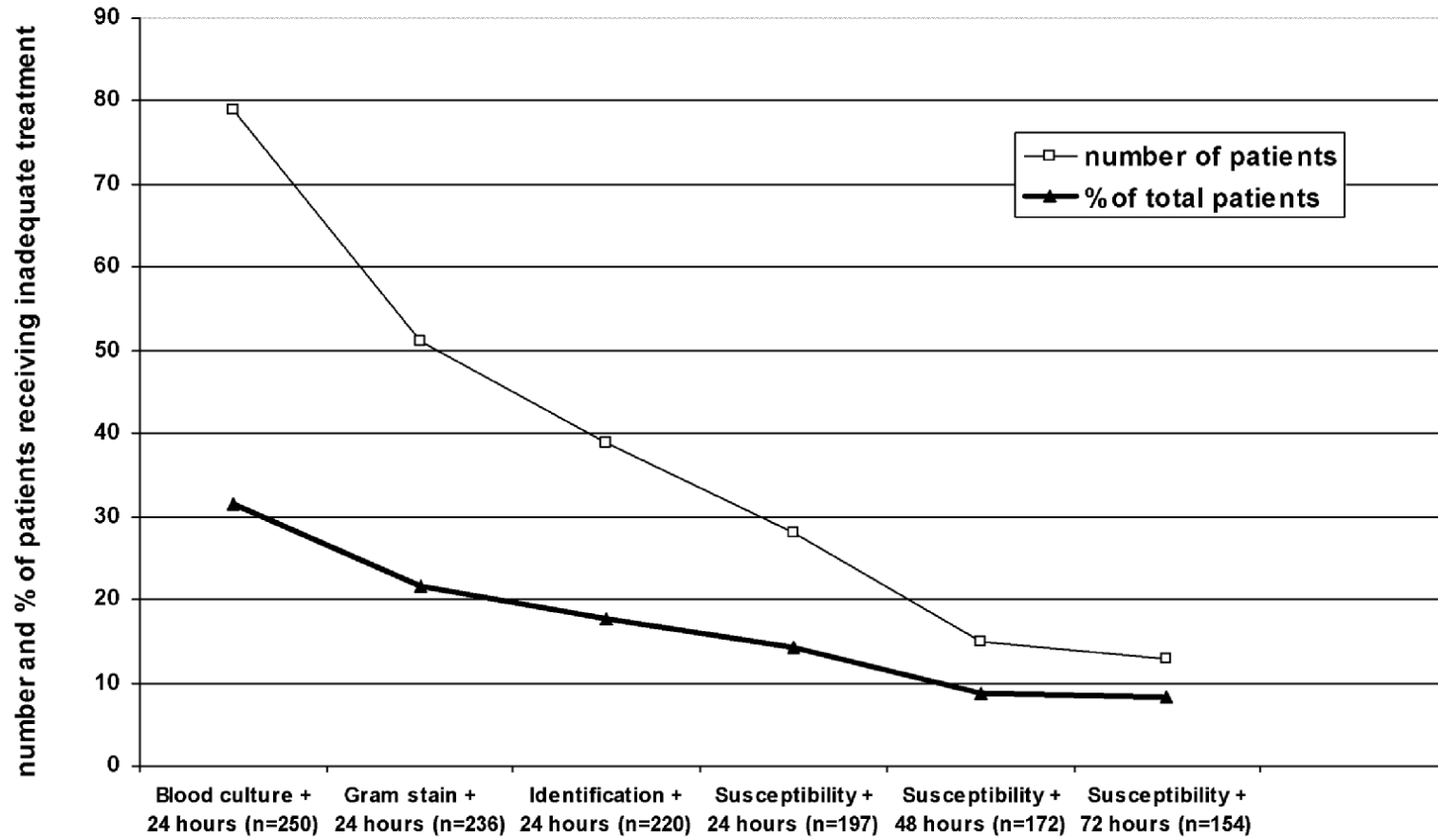
482

483   NOTE. Denominator changes due to patient discharge or death.