TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 29-33
© TÜBİTAK
doi:10.3906/sag-1508-102

Pooled analysis of 899 nosocomial meningitis episodes from Turkey

Oğuz Reşat SİPAHİ[1], Arzu NAZLI ZEKA[2,*], Meltem TAŞBAKAN[1], Hüsnü PULLUKÇU[1], Bilgin ARDA[1], Tansu YAMAZHAN[1], Hilal SİPAHİ[3], Sercan ULUSOY[1]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Ege University, İzmir, Turkey
[2]Bilecik State Hospital, Bilecik, Turkey
[3]Bornova District Directorate of Health, İzmir, Turkey

Received: 19.08.2015 • **Accepted/Published Online:** 17.04.2016 • **Final Version:** 27.02.2017

Background/aim: Healthcare-associated meningitis (HCAM) is a relatively rare entity with significant morbidity and mortality. The aim of this study was to systematically review the Turkish medical literature for acute nosocomial meningitis.

Materials and methods: One national (ULAKBİM) and two international (www.scopus.com and www.pubmed.com) databases were searched. In addition, abstracts of four national congresses held between 2004 and 2013 were searched for reports for HCAM meningitis.

Results: Data for 899 HCAM meningitis episodes were obtained from 24 reports. In terms of clinical findings, 177 of 216 (81.9%) had fever (>38 °C), 55 of 64 (85.9%) had high CRP levels, 105 of 132 had leukocytosis (>10,000/mm^3), and 241 of 759 had shunt infection. Cerebrospinal fluid culture yielded a pathogen in 689 of 872 nosocomial meningitis episodes. The most common pathogen was *Acinetobacter* spp. (30.7%), followed by coagulase-negative staphylococci (21.2%) and *Staphylococcus aureus* (19%). Carbapenem resistance was reported in 18 of 48 (37.5%) *Acinetobacter* spp. Overall mortality was 160/593 (27%). Pathogen-specific mortality was 55.5% (30/54) for *A. baumannii* whereas it was 18.9% (7/37) for *S. aureus* and 2/17 (11,7%) for MRSA.

Conclusion: Nosocomial meningitis is still a serious and highly fatal disease. More preventive measures should be sought to further decrease HCAM meningitis and the mortality/morbidity related to it.

Key words: Nosocomial infections, healthcare-associated infections, hospital-acquired infections, nosocomial meningitis, healthcare-associated meningitis

1. Introduction

Despite developments in antimicrobial agents and intensive care units, meningitis as well as nosocomial or healthcare-associated meningitis (HCAM) is still associated with significant mortality and morbidity (1–3). Several studies of epidemiological or clinical features and prognostic factors in adults with HCAM have been performed; however, nearly all are retrospective and relatively small in size and many are from developed countries (4–8). Studies from Turkey are also retrospective and have the disadvantage of low patient numbers (9–32). The aim of this study was to systematically review the medical literature from Turkey for acute adult purulent meningitis between 1998 and 2013.

2. Materials and methods

To perform the review, published series were searched in one national database, the ULAKBİM Turkish medical literature database (http://uvt.ulakbim.gov.tr/uvt/), and two international databases (www.scopus.com and www.pubmed.com). In addition to these databases, abstracts of congresses held between 2004 and 2013 by the Turkish Clinical Microbiology and Infectious Diseases Specialists Association (Turkish acronym: EKMUD), the Turkish Clinical Microbiology and Infectious Diseases Association (KLİMİK), the Antibiotic and Chemotherapy Association (ANKEM), and the Turkish Society of Hospital Infection Control and Prevention (HİDER) were searched for reports of nosocomial meningitis. For a more comprehensive review, articles cited in references from these sources have also been included. The key word for the national database was 'meningitis'. Key words used for Scopus and PubMed were 'meningitis and Turkey and (nosocomial or healthcare associated or hospital acquired)'. All abstracts found in databases or congress proceeding books were analyzed by two separate investigators.

For studies that were both published and presented at congresses, only the published article was taken into

* Correspondence: arzunazli@hotmail.com

consideration. In the case of presentations from a single study with overlapping periods, the study covering the longer duration was chosen. The following articles were excluded: 1) articles published before 1998; 2) community-acquired meningitis series; 3) chronic meningitis case reports/series; 4) aseptic meningitis series; 5) chronic meningitis series; 6) case reports or series with less than 5 patients, and 7) pediatric series.

3. Results

Data for 858 patients with a diagnosis of 899 nosocomial meningitis episodes were obtained from 24 reports (19 articles, 5 congress abstracts) in our study (9–32). All reports used the CDC criteria for nosocomial meningitis (33). Of the 19 published articles, nine were in peer-reviewed medical journals indexed in national databases and 10 in peer-reviewed journals indexed in international databases.

Sex was reported for 583 patients (45.1% female, 54.9% male). The pooled mean age was 26.5 (n = 795). As underlying diseases, 27.9% (188/672) had intracranial mass, 17.2% (111/642) had intracranial bleeding, 6.2% (35/565) had aneurysms, and 8.4% (57/682) had trauma. Additionally, 32.8% (109/332) had a coinfection in another body site.

In terms of clinical findings, 177 out of 216 (81.9%) had fever (>38 °C) and 23 out of 103 (22.3%) had headache. Twenty-seven out of 111 (24.3%) had stiffness of the neck. In addition, 72 out of 112 (64.2%) had vomiting or nausea. Disturbances of consciousness were present in 78 out of 116 (67.2%), while 85.9% (55/64) had high CRP levels and 105 of 132 (79.5%) had leukocytosis (>10,000/mm^3). Furthermore, 31.8% (241 of 759) had shunt infection.

Cerebrospinal fluid culture yielded a pathogen in 79% (689/872) of the nosocomial meningitis episodes (Table). In addition, 22.5% had concomitant bacteremia. The most common pathogen was *Acinetobacter* spp. (30.7%), followed by coagulase-negative staphylococci (21.2%) and *S. aureus* (19%). Gram staining was reported to be positive in 23 out of 58 (39.6%) cases. Carbapenem resistance was reported in 18 of 48 (37.5%) *Acinetobacter* spp. meningitis strains. About 61% (47/77) of *S. aureus* and 80.6% (29/36) *S. epidermidis* meningitis episodes were methicillin-resistant. In 78.1% of shunt infections (100/128) the shunt was removed during the management. Overall mortality was 27% (160/593). Pathogen-specific mortality was 55.5% (30/54) for *A. baumannii* whereas it was 18.9% (7/37) for *S. aureus* and 2/17 (11.7%) for MRSA.

Table. Distribution of pathogens isolated in the CSF cultures of 689 nosocomial meningitis episodes.

Organism	Number*
Acinetobacter spp.	212
Coagulase-negative staphylococci	146
Staphylococcus aureus	131
Pseudomonas aeruginosa	35
Klebsiella spp.	35
Escherichia coli	35
Enterobacter spp.	27
Enterococcus spp.	24
Candida spp.	18
Streptococcus pneumoniae	9
Stenotrophomonas maltophilia	5
Serratia marcescens	4
Citrobacter spp.	2
Burkholderia spp.	2
Beta-hemolytic streptococci	2
Brucella spp.	2
Flavobacterium odoratum	1
Achromobacter xylosoxidans	1
Morganella morganii	1
Aeromonas hydrophila	1
Proteus spp.	1
Corynebacterium amycolatum	1
Haemophilus influenzae	1
Kluyvera spp.	1
Hafnia alvei	1
Aspergillus spp.	1
Total	699

*Ten cases had mixed infections.

4. Discussion

Although HCAM is a relatively small part of healthcare-associated infections (34), it may result in severe consequences such as significant morbidity and mortality. Durand et al. (4) reported that HCAM accounted for 40% of 495 acute bacterial meningitis episodes in a 27-year period. This rate may increase in centers with a higher number of invasive hospital practices.

In contrast to community-acquired acute purulent meningitis, where pneumococci and meningococci are the dominating pathogens (1–3), the major causative agents in HCAM are usually gram-negative bacilli including *Pseudomonas aeruginosa*, *Acinetobacter* spp., or *Enterobacteriaceae* and gram-positive cocci such as staphylococci or enterococci. The overall rate of etiological agents yielded by bacterial cultures is also higher in nosocomial meningitis than community-acquired meningitis (35), which is probably due to the fact that the

common bacteria are easier to grow and they are usually multidrug-resistant, less inhibited by the antibiotics used commonly in the community. In the presented study, overall mortality was 27%, comparable to other nosocomial meningitis series (5,6,8).

The most common bacterial agent causing HCAM differs from country to country: in the Netherlands, pneumococci (5); MRSA in Taiwan (6); *E. coli* in the United States (4); coagulase-negative staphylococci in Korea (8); and MSSA in France (7). These major differences are probably due to infection control measures and/or the spectrum of neurosurgical operation types. In the presented study the most common etiologic agent was *Acinetobacter* spp. In Turkey *Acinetobacter* spp. and *S. aureus* are among the most common causes of overall healthcare-associated infections in many hospitals.

In our study the pooled carbapenem resistance rate was 37.5% and the methicillin resistance rate in coagulase-negative staphylococci was 81%. In addition, carbapenem-resistant *A. baumannii* and MRSA are endemic in many hospitals. Fifty-percentile carbapenem resistance rate in *A. baumannii* and MRSA strains causing healthcare-associated infections in Turkish tertiary-care educational university hospitals were 87.3% and 43.2% in 2012, respectively (http://www.saglikaktuel.com/d/file/uhesa-analiz-2012.pdf). Fifty-percentile carbapenem-resistant strains are almost always resistant to the commonly used first-line antimicrobial agents ceftazidime, cefepime, and meropenem in the empirical treatment of HCAM (1–3,36,37). This is probably the reason for the quite high mortality of 55.5% in carbapenem-resistant *A. baumannii* meningitis, which also suggests colistin as a first-line therapy in empirical antibiotherapy. Probably since first-line empirical therapy usually includes vancomycin (1–3), the mortality rate of vancomycin was lower in MRSA meningitis (11.7%).

In the presented study, two cases of *Brucella* spp. HCAM were reported. *Brucella* spp. infections as well as neurobrucellosis are endemic in Turkey (38,39). Recently, Mermer et al. also reported a *Brucella* spp. shunt infection (39). As with the two cases reported in this pooled analysis, we can suggest that one should keep in mind the possibility of shunt infections with such organisms in communities with certain endemic infections such as brucellosis (40).

When we compared our results in terms of symptoms with the results of a pooled analysis of nonnosocomial adult acute purulent meningitis (35), fever (81.9% vs. 79.8%), disturbances of consciousness (67.2% vs. 57.6%), nausea (64.2% vs. 69.7%), and leukocytosis (79.5% vs. 82.7%) were nearly as common. However, neck stiffness (24.5% vs. 89.8%) and headache (22.3% vs. 88.2%) were lower, which is probably due to the predominance of shunt infections or CSF leakage, which does not cause a prominent increase in the cerebrospinal fluid pressure (2,35).

Pooled analysis is advantageous in understanding the epidemiology of rare diseases and syndromes such as fever of unknown origin, meningitis, and mucormycosis (35–42). While pooling the data, the inclusion criteria are important. Retrospective studies have the disadvantage of depending on retrospective hospital records. Although the studies included in this pooled analysis used the CDC definitions (33) for nosocomial meningitis, they all used retrospective clinical data. Another important disadvantage of our study is the heterogeneity of the data. Because of this heterogeneity, the ratios in different variables have different denominators. Although all centers were tertiary-care educational hospitals, possible double reports of a single patient from two different centers cannot be excluded. Since abstracts of the congresses held before 2004 could not be reached thoroughly, abstracts between 1998 and 2003 could not be included in the study. In spite of these disadvantages, to our knowledge this is the first pooled analysis on this topic gathering the most data and major clues about the epidemiology and clinical findings in HCAM in Turkey as well as the world.

In conclusion, the presented data show that HCAM is associated with 27% mortality. *Acinetobacter* spp. seem to be the most important pathogens in HCAM in Turkey. Carbapenem-resistant *A. baumannii* meningitis is associated with a mortality of 55.5% and MRSA with 11.7%. Hence, colistin may be an important antibiotic in centers with high carbapenem resistance rates. In order to identify epidemiologic changes, it is necessary to create an appropriate national registration system with fewer bureaucratic entities. Finally, effective infection control measures regarding prevention of HCAM are urgently needed.

Acknowledgment

We would like to thank the European Study Group for Infections of the Brain (ESGIB) for their collaboration in analysis and interpretation of the data.

References

1. Van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. N Engl J Med 2010; 362: 146-154.

2. Bardak-Özcem S, Sipahi OR. An updated approach to healthcare-associated meningitis. Expert Rev Anti Infect Ther Mar 2014; 12: 333-342.

3. Bardak-Özcem S, Sipahi OR. Approach to hospital-acquired and methicillin-resistant Staphylococcus aureus meningitis. Mediterr J Infect Microbes Antimicrob 2013; 2: 1.

4. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS. Acute bacterial meningitis in adults, a review of 493 episodes. N Engl J Med 1993; 328: 21-28.

5. Weisfelt M, Van de Beek D, Spanjaard L, de Gans J. Nosocomial bacterial meningitis in adults. A prospective series of 50 cases. J Hosp Infect 2007; 66: 71-78.

6. Wang KW, Chang WN, Huang CR, Tsai NW, Tsui HW, Wang HC, Su TM, Rau CS, Cheng BC, Chang CS et al. Post-neurosurgical nosocomial bacterial meningitis in adults: microbiology, clinical features, and outcomes. J Clin Neurosci 2005; 12: 647-650.

7. De Bels D, Korinek AM, Bismuth R, Trystram D, Coriat P, Puybasset L. Empirical treatment of adult postsurgical nosocomial meningitis. Acta Neurochir 2002; 144: 989-995.

8. Kim HI, Kim SW, Park GY, Kwon EG, Kim HH, Jeong JY, Chang HH, Lee JM, Kim NS. The causes and treatment outcomes of 91 patients with adult nosocomial meningitis. Korean J Intern Med 2012; 27: 171-179.

9. Sacar S, Turgut H, Toprak S, Çırak B, Coskun E, Yılmaz O, Tekin K. A retrospective study of central nervous system shunts infections diagnosed in a university hospital during 4-year period. BMJ Infect Dis 2006; 6: 43.

10. Erdem I, Hakan T, Ceran N, Akcay SS, Kucukercan M, Berkman MZ, Goktas P. Clinical features, laboratory data, management and risk factors that affect the mortality in patients with postoperative meningitis. Neurol India 2008; 56: 433-437.

11. Metan G, Alp E, Aygen B, Sumerkan B. *Acinetobacter baumannii* meningitis in post-neurosurgical patients: clinical outcome and impact of carbapenem resistance. J Antimicrob Chemother 2007; 60: 197-199.

12. Fisgin NT, Tanyel E, Ulus A, Tülek N. Beyin cerrahi kliniğinde hastaya dayalı aktif sürveyansın önemi. İnfeksiyon Dergisi 2008; 22: 135-140 (in Turkish).

13. Sari T, Oral B, Ertem G, Tülek N. Çoklu ilaca dirençli *Acinetobacter baumannii* ile oluşan menenjit olgularında intravenöz ve intratekal kolistin tedavisi (Poster P095). Hastane İnfeksiyonları Dergisi 2010; 14: 226 (in Turkish).

14. Sardan YC, Yıldırım A, Yıldırım G, Bostancı H, Şahin H, Ünal S. Bir nozokomiyal menenjit salgınının incelenmesi (Poster P04). Hastane İnfeksiyonları Dergisi 2004; 8 (Ek 2): 3 (in Turkish).

15. Erbektaş I, Lale S, Kıraz S, Köse T, Palabıyıkoğlu I, Tekeli E, Çokça F, Akan O, Unal N. Nozokomiyal menenjitler: 1993-2002 (Poster P63). Hastane İnfeksiyonları Dergisi 2004; 8 (Ek 2): 39 (in Turkish).

16. Sacar S, Asan A, Mete E, Çaylak SD, Cırak B, Akalın S, Aybek H, Turgut H. Şant enfeksiyonlarının değerlendirilmesi (Poster P12-04). In: 15th KLİMİK Kongresi 2011; 23–27 March 2011; Manavgat, Antalya, Turkey (in Turkish).

17. Köseoğlu O, Salmanzadeh-Ahrabi S, Hasçelik G, Günalp A. Nosocomial bacterial meningitis in adult hospital of Hacettepe University Medical Faculty. Türk Mikrobiyol Cem Derg 2000; 31: 187-191 (in Turkish with abstract in English).

18. Avcı M, Özgenç O, Coşkuner A, Mermut G, Güloğlu G. İzmir Eğitim ve Araştırma Hastanesi'nde 2000-2005 yılları arasında izlenen nozokomiyal menenjitler (Poster P050). Hastane İnfeksiyonları Dergisi 2006; 10 (Ek 1): 36 (in Turkish).

19. Sipahi OR, Bardak S, Turhan T, Arda B, Pullukcu H, Ruksen M, Aydemir S, Dalbasti T, Yurtseven T, Zileli M et al. Linezolid in the treatment of methicillin-resistant staphylococcal post-neurosurgical meningitis: a series of 17 cases. Scand J Infect Dis 2011; 43: 757-764.

20. Öktem İS, Menkü A, Özdemir A. When should ventriculoperitoneal shunt placement be performed in cases with myelomeningocele and hydrocephalus? Turk Neurosurg 2008; 18: 387-391.

21. Telhan L, Çavuşoğlu F, Müslüman M, Türkmenoğlu O, Çetinkaya F. Etiologic and prognostic assessment of children with ventriculoperitoneal shunt infections. Journal of Pediatric Infection 2010; 4: 100-103 (in Turkish with abstract in English).

22. Arslan M, Eseoglu M, Gudu BO, Demir I, Kozan A, Gokalp A, Sosuncu E, Kiymaz N. Comparison of simultaneous shunting to delayed shunting in infants with myelomeningocele in terms of shunt infection rate. Turk Neurosurg 2011; 21: 397-402.

23. Yılmaz A, Haci AG, Müslüman AM, Çolak I, Şahin Y, Aydın Y. Ventriculoperitoneal shunt dysfunctions. Turk Neurosurg 2006; 16: 150-155.

24. Turgut N, Alabaz D, Erbey F, Kocabas E, Erman T, Alhan E, Aksaray N. Cerebrospinal fluid shunt infections in children. Pediatr Neurosurg 2005; 41: 131-136.

25. Palabiyikoglu I, Tekeli E, Cokca F, Akan O, Unal N, Erberktas I, Lale S, Kiraz S. Nosocomial meningitis in a university hospital between 1993 and 2002. Hosp Infect 2006; 62: 94-97.

26. Kurtaran B, Candemir A, Taşova Y, İnal AS, Yılmaz DM, Kömür S, Sarıtürk C, Aksu H. Cerrahi sonrası gelişen menenjitlerin risk faktörleri ve sonuçları. Flora 2011; 16: 160-168 (in Turkish).

27. Bulut C, Tekiner A, Yetkin A, Hatipoğlu ÇA, Bayar MA, Tülek N. Beyin cerrahi girişimleri sonrası gelişen hastane kökenli menenjitlerin değerlendirilmesi. Hastane İnfeksiyonları Dergisi 2005; 9: 218-224 (in Turkish).

28. Saba R, İnan D, Günseren F, Özçelik FT, Mamıkoğlu L. Akdeniz Üniversitesi Hastanesi'nde nozokomiyal menenjitler. Hastane İnfeksiyonları Dergisi 2000; 4: 47-50 (in Turkish).

29. Naz H, Aykın N, Çağlayan Çevik F. Hospital acquired central nervous system infections: evaluation of 15 cases. ANKEM Derg 2009; 23: 82-85 (in Turkish with abstract in English).

30. Çelik İ, Erol FS, Cihangiroğlu M, Akdemir İ, Tiftikçi M. Evaluation of the ventriculoperitoneal shunt infection cases. ANKEM Derg 2003; 17: 60-64 (in Turkish with abstract in English).

31. Arda B, Yamazhan T, Sipahi OR, Islekel S, Buke C, Ulusoy S. Meningitis due to methicillin-resistant *Staphylococcus aureus* (MRSA): review of 10 cases. Int J Antimicrob Agents 2005; 25: 414-418.

32. Dizbay M, Güzel Tunçcan Ö, Arman D, Baş S, Gürsoy A, Aktaş F. Factors associated with mortality in nosocomial central nervous system infections. ANKEM Derg 2011; 25: 6-11 (in Turkish with abstract in English).

33. Garner JS, Jarvis WR, Emori TG, Horon TC, Hughes JM. CDC definitions for nosocomial infections. In: Olmsted RN, editor. APIC Infection Control and Applied Epidemiology: Principles and Practice. St. Louis, USA: Mosby; 1996. pp. A1-A20.

34. Erdem HA, Sipahi OR, Kepeli N, Dikis D, Deniz-Kucukler N, Aksoy B, Korkmaz N, Barık ŞA, Arda B, Özinel MA et al. Point prevalence of hospital-acquired infections in Ege University Hospital. Mediterr J Infect Microbes Antimicrob 2015; 4: 12.

35. Arda B, Sipahi OR, Atalay S, Ulusoy S. Pooled analysis of 2,408 cases of acute adult purulent meningitis from Turkey. Med Princ Pract 2008; 17: 76-79.

36. Aktuğ-Demir N, Özcan M, Özcimen S, Kacar F, Korkmaz F, Güney I. Atypical *Acinetobacter baumannii* meningitis: case report. Mediterr J Infect Microbes Antimicrob 2014; 3: 6.

37. Zeka AN, Poirel L, Sipahi OR, Bonnin RA, Arda B, Ozinel M, Ulusoy S, Bor C, Nordmann P. GES-type and OXA-23 carbapenemase-producing *Acinetobacter baumannii* in Turkey. J Antimicrob Chemother 2014; 69: 1145-1146.

38. Uysal S, Dana F, Işıkgöz-Taşbakan M, Kismali E, Sipahi OR, Pullukçu H, Yamazhan T, Ulusoy S. Evaluation of hepatosplenomegaly and liver function tests in 102 brucellosis cases. Mediterr J Infect Microbes Antimicrob 2014; 3: 24.

39. Çalık Ş, Gökengin D. Human brucellosis in Turkey: a review of the literature between 1990 and 2009. Turk J Med Sci 2011; 41: 549-555.

40. Mermer S, Sipahi OR, Aydemir S, Tasbakan M, Pullukcu H, Arda B, Yamazhan T, Ulusoy S. *Brucella melitensis* shunt infection. Neurol India 2013; 61: 670-671.

41. Sipahi OR, Senol S, Arsu G, Pullukcu H, Tasbakan M, Yamazhan, Arda B, Ulusoy S. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990-2006. Med Sci Monit 2007; 13: 318-322.

42. Zeka AN, Taşbakan M, Pullukçu H, Sipahi OR, Yamazhan T, Arda B. Evaluation of zygomycosis cases by pooled analysis method reported from Turkey. Mikrobiyol Bul 2013; 47: 708-716.