Intensive Care Med (2003) 29:1868–1870
DOI 10.1007/s00134-003-1934-5

EDITORIAL

Werner Zimmerli

Acute bacterial meningitis: time for a better outcome

Received: 4 July 2003
Accepted: 8 July 2003
Published online: 2 August 2003

W. Zimmerli (✉)
Medical University Clinic,
Kantonsspital Liestal,
4410 Liestal, Switzerland
e-mail: werner.zimmerli@unibas.ch
Tel.: +41-61-9252180
Fax: +41-61-9252804

Between 1935 and the mid-fifties, the fatality rate from acute bacterial meningitis decreased impressively from 85% to 37% [1]. This striking reduction was clearly due to the introduction of antimicrobial agents [1]. However, between the sixties and the mid-nineties, the prognosis did not substantially improve and the mortality rate remained roughly stable at 20–25% [1, 2, 3, 4, 5, 6, 7]. It is unclear why there was no further improvement of the prognosis during three decades, despite new and more potent antibiotics such as third generation cephalosporins (cetriaxone, cefotaxime) and despite broader availability of, and more sophisticated, critical care medicine.

During the past two decades, important progress has been made in understanding the pathogenesis of meningitis [8, 9, 10]. The mechanisms of neuro-invasion and inflammation have been elucidated. The pathogenesis of cortical necrosis on the one hand and hippocampal apoptosis on the other have been studied. It has been shown that oxidative radicals play a crucial and noxious role for cerebral blood flow and consecutive cortical brain damage. In addition, the complex effects of nitric oxide have been analyzed. Interestingly, depending on the stage of bacterial meningitis, inhibition of nitric oxide synthase can either diminish or aggravate cerebral blood flow and consecutively result in brain damage [8 for review]. Since hippocampal apoptosis leads to neurologic sequelae or even death, the underlying mechanisms of apoptosis have been studied. In brief, inhibition of matrix metalloproteinases and TNF-alpha converting enzyme was experimentally beneficial, whereas corticosteroids and radical oxygen scavengers even aggravated apoptosis [11, 12]. In view of these complex effects, even in the well defined setting of experimental pneumococcal meningitis, it is not astonishing that these experimental data have not yet translated into improved outcome of meningitis in humans.

Table 1 summarizes the fatality rates of patients with meningitis during various successive time periods from

Table 1 Fatality rates of bacterial meningitis during the last 40 years

Time period		Overall (%)	Due to *Streptococcus pneumoniae* (%)	Author
1962–88		25	28.5	Durand et al. [2]
1970–95		27	Not reported	Aronin et al. [3]
1978–81		13.2	26.3	Schlech et al. [4]
1975–94		19.7	25.9	Sigurdardottir et al. [5]
1985–96		18	26	Hussein et al. [6]
1994–95		13.3	21	Schuchat et al. [7]
1993–01	Control	15	34	De Gans et al. [13]
	Dexamethasone	7	14	
1995–00		10.9	<16*	Flores-Cordero et al. [14]

*16% unfavorable outcome (neurologic sequelae and death)

1962–2001. Whereas the overall mortality varied by up to 50% (13.2–27.0%) between 1962–1995, regardless of the study period, mortality due to pneumococcal meningitis remained quite stable, ranging between 21% and 28% during the three decades. Thus, novel antibiotics, knowledge in pathogenesis and better supportive care did not translate into measurably better outcome. It is conceivable that improvements over time in the management of meningitis are not visible in terms of an overall fatality rate, due to the selective decrease of those types of meningitis with good prognosis. The case fatality rate of meningitis due to *Haemophilus influenzae* and *Neisseria meningitidis* is low, namely 6% and 3%, respectively, whereas mortality due to pneumococcal and listerial meningitis is 21% and 15%, respectively [7]. Since vaccination against *Haemophilus influenzae* and *Neisseria meningitidis* is widely used nowadays, these etiologies have become rare. In contrast, the prevalence of etiologies associated with higher fatality rates (*Streptococcus pneumoniae, S. aureus, Listeria monocytogenes*) have not decreased. In addition, increasing resistance to beta-lactams of strains causing pneumococcal meningitis may counteract the improvement of supportive care. Thus, decreasing the overall fatality rate of meningitis now requires either an efficacious prophylaxis against high-risk meningitis (e.g. conjugated pneumococcal vaccine against a broad spectrum of capsular types) or better management of pneumococcal meningitis.

The prospective, randomized, double-blind trial of adjuvant therapy with dexamethasone in adults with bacterial meningitis shows that there is room for improved management (Table 1) [13]. Patients who profit from dexamethasone (10 mg every 6 h over 4 days, starting before or at the time of antibiotic therapy) are those with pneumococcal meningitis and with a Glasgow Coma Scale (GCS) score between 8–11. In this issue of *Intensive Care Medicine*, Flores-Cordero et al. [14] report their data of a prospective observational study of adult patients with acute community-acquired bacterial meningitis. They report an impressively low overall fatality rate of 10.9%. Their rate of meningitis without identified pathogen was quite high (26.5%), probably due to the frequent use of antibiotics before microbiological sampling (29.6%). However, even the rate of unfavorable outcome (neurologic sequelae and death) of patients with pneumococcal meningitis was very low, at 16%, despite the fact that 12% of the isolates were non-susceptible to cefotaxime.

In their study, significant risk factors for adverse outcome were age over 50 years, neurologic abnormalities at admission, as well as a GCS of 10 or less and an APACHE II score higher than 13. Therefore, the good prognosis reported by Flores-Cordero et al. [14] was probably due to three factors: (1) low median age (46 years compared to 57 years in the study of Aronin et al. [3], (2) low initial APACHE II score of 11.5 and (3) relatively high initial GCS of 11. Whereas the good initial clinical status was obviously due to a very high degree of suspicion by the general practitioner and the emergency room physician, the potential role of other factors cannot be answered with the data of this study. However, it is possible that rapid antimicrobial therapy was crucial, as suggested by Aronin et al. [3]. Unfortunately, the role of steroids and of supportive care in the intensive care unit cannot be estimated from this study, since the protocol did not control for these factors.

Despite the fact that the fatality rate of bacterial meningitis is finally decreasing, there is still need for improvement. Rapid hospitalization in cases of clinical suspicion of meningitis, microbiological sampling without delay, rapid treatment of selected patients with steroids, initiation of antimicrobial therapy as soon as possible and ICU hospitalization of patients with high APACHE II score or low GCS should be standard care. Whether further knowledge about the pathogenesis will result in successful adjuvant treatment modalities remains to be proven in clinical studies.

References

1. Finland M, Barnes MW (1977) Acute bacterial meningitis at Boston City Hospital during 12 selected years, 1935–1972. J Infect Dis 136:400–415
2. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, Swartz MN (1993) Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 328:21–28
3. Aronin SI, Peduzzi P, Quagliarello VJ (1998) Community-acquired bacterial meningitis: risk stratification, adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 129:862–869
4. Schlech WF III, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV (1985) Bacterial meningitis in the Unites States 1978 through 1981. JAMA 253:1749–1754
5. Sigurdardóttir B, Björnsson OM, Jonsdóttir KE, Erlendsdóttir H, Gudmundsson S (1997) Acute bacterial meningitis in adults. A 20-year overview. Arch Intern Med 157:425–430
6. Hussein AS, Shafran SD (2000) Acute bacterial meningitis in adults. A 12-year review. Medicine (Baltimore) 79:360–368
7. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, Lefkowitz L, Bradley A, Perkins BA for the Active Surveillance Team (1997) Bacterial meningitis in the United States in 1995. N Engl J Med 337:970–976
8. Meli DN, Christen S, Leib SL, Täuber MG (2002) Current concepts in the pathogenesis of meningitis caused by *Streptococcus pneumoniae*. Curr Opin Infect Dis 15:253–257

9. Brandtzaeg P, Deuren M (2002) Current concepts in the role of the host response in Neisseria meningitidis septic shock. Curr Opin Infect Dis 15:247–252
10. Echchannaoui H, Frei K, Schnell Ch, Leib SL, Zimmerli W, Landmann R (2002) Toll-like receptor 2-deficient mice are highly susceptible to *Streptococcus pneumoniae* meningitis because of reduced bacterial clearing and enhanced inflammation. J Infect Dis 186:798–806
11. Leib SL, Clements JM, Lindberg RL, Heimgartner C, Loeffler JM, Pfister LA, Täuber MG, Leppert D (2001) Inhibition of matrix metalloproteinases and tumor necrosis factor alpha converting enzyme as adjuvant therapy in pneumococcal meningitis. Brain 124:1734–1742
12. Loeffler JM, Ringer R, Hablützel M, Täuber MG, Leib SL (2001) The free radical scavenger alpha-phenyl-tert-butyl nitrone aggravates hippocampal apoptosis and learning deficits in experimental pneumococcal meningitis. J Infect Dis 183:247–252
13. Gans J, Beek D (2002) Dexamethasone in adults with bacterial meningitis. N Engl J Med 347:1549–1556
14. Flores-Cordero JM, Amaya-Villar R, Rincón-Ferrari MD, Leal-Noval SR, Garnacho-Montero J, Llanos-Rodriguez AC, Murillo-Cabezas F (2003) Acute community-acquired bacterial meningitis in adults admitted to the ICU: clinical manifestations, management and prognostic factors. Intensive Care Med (http://dx.doi.org/10.1007/s00134-003-1935-4)