

# Clinico-epidemiological Characteristics of Children with Infectious Meningitis at Nishtar Medical Hospital

Dr. Muhammad Wajahat Gohar Qureshi Dr. Muhammad Usman Hashmi Dr. Muhammad Omar Salman House Officer Nishtar Hospital Multan

### **Abstract**

### Objective:

This study aims to determine the common Clinico-epidemiological Characteristics of Patients suffering from infectious meningitis presenting at Nishtar medical university hospital Multan, Pakistan.

## Study design:

Descriptive cross-sectional study

# Place and duration of study:

Pediatric department, Nishtar Hospital Multan the duration of the study was February 01, 2016 to January 31, 2017.

#### Method

The study comprised of 172 patients. All the children of age 1 month to 12 years with suspected meningitis presenting to Pediatric Department Nishtar Hospital, Multan were included in our study. The patients who were critically ill or immune compromised were not included in the study. The cases in which the parents did not give consent were also excluded. The written informed consent was taken from the parents. All these cases were evaluated by detailed history, thorough physical examination and the necessary investigations. All the demographic data and other variables related to clinico-epidemiological features were measured and recorded using a specifically designed performa. The data were analyzed by using computer program SPSS 21 version.

## Result

Of the 154 patients included in the final analysis, 98 (63.6%) were females and 56 (36.4%) males. The age ranged from 1 month to 12 years with a median of 31 months (6.00 - 72.50). Seventy-five percent of them were below 5 years. On the basis of investigations, bacterial meningitis was diagnosed in 91, viral meningitis in 27, tuberculous meningitis in 21 and cryptococcal meningitis in 15 patients. The most common clinical presentations of meningitis were fever, vomiting, headache, irritability, neck stiffness and altered level of consciousness. While the photophobia and fits were less common. The GCS score was more than 13 in 109 patients (70.8%) while less than eight GCS score was observed in 45 children (29.2%). Most of the complications were observed in the initial 36 hours of admission. The commonly observed complications were an altered level of sensorium, seizure, and shock. The minimum length of hospitalization was one day and the maximum was 36 days with median (IQR) of 12 days (4-15). The mortality was observed in 22 patients (14.3%) of Pediatric Medicine Department.

# Conclusion

Meningitis is a highly morbific and fatal central nervous system infection in children population. It is associated with life-threatening complications and exhibits highly diverse clinical course with a very non-specific sign and symptoms. Younger children of rural areas are highly prone to fall a victim to this lethal disease. By vaccinating the children population against causative agents of meningitis, we can reduce the burden of disease.

**Keywords:** Meningitis. Children. Clinico-epidemiological features.

### Introduction

Infections of the central nervous system are life-threatening. Meningitis is an infection involving the meninges of the brain and subarachnoid space. This infectious disease may result in impaired consciousness, seizures, increased intracranial pressure and stroke <sup>1</sup>. It is estimated that approximately 70 % of meningitis cases occur in children under the age of 5 and in the elderly people over the age of  $60^2$ . In the United States, bacterial meningitis affects about 4,000 people each year, and viral meningitis affects about 10 people in  $100,000^3$ . Bacterial meningitis incidence in children of tropical countries such as Africa and Asia is very high. A careful review of the recent medical literature reveals that the rate of incidence in these countries is 25 cases per  $100\,000$  children <sup>4</sup>. However, the incidence rate in the United States and the United Kingdom is 0.56 per  $100\,000$  and 1-3 per  $100\,000$  respectively in children aged 2-10 years<sup>5,6</sup>. Exact estimates and epidemiology of infectious meningitis are lacking in Pakistan. But a much higher burden of disease is considered in the countries like Pakistan. A huge load of this infectious disease results in increased rate of morbidity, mortality and economic burden.

Meningitis is usually characterized by fever, headache, intolerance to light and sound, and neck stiffness. The etiological factors for this central nervous system infections differ greatly by a change in geographical area



and age group<sup>7</sup>. The studies have shown that bacterial meningitis is responsible for about 30%–40% of central nervous system infections<sup>6</sup>. The remaining 60-70% is due to other etiologies such as viral meningitis, cryptococcal meningitis, brain abscess, tuberculosis meningitis, tuberculoma, and others<sup>8</sup>. Consequently, meningitis is considered a leading cause of neurological dysfunction. Hence, it requires a comprehensive management plan with special focus on the eradication of the specific etiological factor. Unfortunately, both the epidemiology of meningitis and the sensitivity to various groups of antibiotics are changing as a result of widespread misuse of antimicrobials. The data regarding the specific epidemiology and clinical presentation of meningitis in Pakistani children, and the susceptibility of causative microbes to various antimicrobial groups is quite inconclusive and controversial <sup>9</sup>. Currently, the available medical literature is quite insufficient to address this burning question in a comprehensive way. So the present study aims to determine the common clinicoepidemiological features of children suffering from infectious meningitis.

### **Material and Method**

This descriptive cross-sectional study was conducted at Department of Pediatric Medicine, Nishtar Hospital Multan, Pakistan. The duration of the study was February 01, 2016 to January 31, 2017. The study was comprised of 296 patients.

Inclusion criterion:

Children of age 1 month to 12 years who presented with suspected meningitis.

Exclusion criteria:

- ✓ Critically ill patients.
- ✓ Patients who were immune compromised.
- ✓ Patients having no clear final diagnosis.
- ✓ Patients whose parents not giving consent.

All the children of age 1 month to 12 years with suspected meningitis presenting to Pediatric Medicine Department, Nishtar Hospital Multan, Pakistan were included in our study. Written informed consent was taken from parents. All these cases were evaluated by detailed history, thorough physical examination and the necessary investigations. According to needs of patients, various laboratory investigations and imaging studies e.g. complete blood count, renal parameters, liver function tests, serum electrolytes, chest X-ray, CT scan brain, lumbar puncture for cerebrospinal fluid analysis and culture sensitivity were done for the further evaluation of the disease. Different variables such as age, sex, residential area, prominent symptoms, and the grades of the complications were recorded in a specifically designed performa. The data were analyzed by using computer program SPSS 21 version. The descriptive statistics were used to calculate mean  $\pm$  SD for the age of the patients. Frequencies and percentages were calculated for all the variables included in the study.

## Results

A total of 172 patients with clinical suspicion of meningitis were enrolled. Eighteen patients were excluded; out of these eighteen cases, twelve patients did not have infectious meningitis. In two cases, the parents did not give consent, while four patients did not have a clear final diagnosis. Of the 154 patients included in the final analysis, 98 (63.6%) were females and 56 (36.4%) males. The age ranged from 1 month to 12 years with a median of 31 months (6.00 - 72.50). Seventy-five percent of them were below 5 years. On the basis of investigations, bacterial meningitis was diagnosed in 91, viral meningitis in 27, tuberculous meningitis in 21 and cryptococcal meningitis in 15 patients. Out of the 91 patients which were diagnosed as a case of bacterial meningitis, 13(11.83%) had positive cerebrospinal fluid culture. The common presenting complains were fever (n=140, 91%), vomiting (n=76, 49.4%), headache (n=62, 40.3), irritability (n=99, 64.3%), drowsiness (n=47, 30.5%), and photophobia (n=17, 11%). The common signs observed in these patients were neck stiffness (n=43, 27.9%), Kerning's sign (n=22, 14.3%), Brudzincski's sign (n=29, 18.8%), bulging fontanels (n=14, 9%), focal neurological signs (n=11, 7.1%) and dilated poorly reactive pupils (n=4, 2.6%). The GCS score was more than 13 in 109 patients (70.8%), while less than eight GCS score was observed in 45 children (29.2%). Most of the complications were observed in the initial 36 hours of admission, in children less than 5 years of age with bacterial meningitis. The commonly observed complications were an altered level of sensorium, seizure, and shock. Mechanical ventilation was required in 61 (39.6%) and inotropic support in 43 (27.9%) patients. The outcome of meningitis was analyzed in terms of patient survival and length of hospital stay. The minimum length of hospitalization was 1 day and the maximum was 36 days with median (IQR) of 12 days (4-15). As far as the mortality is concerned, it was observed in 22 patients of Pediatric Medicine Department (14.3%).



Table I: Demographic features of patients with meningitis.

rable 1. Demographic features of patients with mennights.	
Variable	N (%)
Age	
< 5 years	116 (75.3)
> 5 years	38 (24.7)
Median(IQR)	31 (6.00-72.50)
Gender	
Male	56 (36.4%)
Female	98 (63.6%)
Residential area	
Rural	127 (82.4)
Urban	27 (17.53)

Table II: Clinical features of patients with meningitis

Diagnosis   Sacterial meningitis   91(59.1)	Table II: Clinical features of patients with meningitis	
Viral meningitis   27(17.53)     Tuberculous meningitis   21 (13.63)     Cryptococcal meningitis   15 (9.7)     Major sign and symptoms   Fever   140 (91)     Vomiting   76 (49.4)     headache   62 (40.3)     Irritability   99 (64.3)     Drowsiness   47 (30.5)     Photophobia   17 (11)     Bulging fontanels   14 (9)     Focal neurological signs   11 (7.1)     Neck stiffness   43 (27.9)     Kerning's sign   22 (14.3)     Brudzincski's sign   29(18.8)     Dilated poorly reactive pupils   4 (2.6)     GCS at presentation   More than thirteen   109 (70.8)     Less than eight   45 (29.2)     Complications   Convulsions   27 (82.5)     Complications   127 (82.5)     Convulsions   99 (64.2)     Shock   56 (36.4)     Mechanical ventilator support   43 (27.9%)     Length of first hospital stay (Days)   Minimum   1     Maximum   36     Median(IQR)   12 days (4-15)     Outcome   Survivors   132 (85.7)	Diagnosis	
Tuberculous meningitis   21 (13.63)	Bacterial meningitis	91(59.1)
Cryptococcal meningitis   15 (9.7)	Viral meningitis	27(17.53)
Major sign and symptoms	Tuberculous meningitis	21 (13.63)
Fever	Cryptococcal meningitis	15 (9.7)
Vomiting	Major sign and symptoms	
headache   62 (40.3)     Irritability   99 (64.3)     Drowsiness   47 (30.5)     Photophobia   17 (11)     Bulging fontanels   14 (9)     Focal neurological signs   11 (7.1)     Neck stiffness   43 (27.9)     Kerning's sign   22 (14.3)     Brudzincski's sign   29 (18.8)     GCS at presentation   More than thirteen   109 (70.8)     Less than eight   45 (29.2)     Complications   Altered level of consciousness   127 (82.5)     Convulsions   99 (64.2)     Shock   56 (36.4)     Mechanical ventilator support   61 (39.6%)     Length of first hospital stay (Days)     Minimum   1     Maximum   36     Median(IQR)   12 days (4-15)     Outcome   Survivors   132 (85.7)	Fever	140 (91)
Irritability   99 (64.3)     Drowsiness   47 (30.5)     Photophobia   17 (11)     Bulging fontanels   14 (9)     Focal neurological signs   11 (7.1)     Neck stiffness   43 (27.9)     Kerning's sign   22 (14.3)     Brudzincski's sign   29 (18.8)     Dilated poorly reactive pupils   4 (2.6)     GCS at presentation   45 (29.2)     Complications   45 (29.2)     Complications   47 (82.5)     Convulsions   48 (27.9)     Mechanical ventilator support   43 (27.9%)     Length of first hospital stay (Days)     Median(IQR)   12 days (4-15)     Outcome   5 (12.5)     Outcome   7 (12.5)     Outcome	Vomiting	76 (49.4)
Drowsiness   47 (30.5)   Photophobia   17 (11)   Bulging fontanels   14 (9)	headache	62 (40.3)
Photophobia   17 (11)   Bulging fontanels   14 (9)	Irritability	99 (64.3)
Bulging fontanels	Drowsiness	
Focal neurological signs	Photophobia	17 (11)
Neck stiffness         43 (27.9)           Kerning's sign         22 (14.3)           Brudzincski's sign         29(18.8)           Dilated poorly reactive pupils         4 (2.6)           GCS at presentation         109 (70.8)           Less than eight         45 (29.2)           Complications         127 (82.5)           Convulsions         99 (64.2)           Shock         56 (36.4)           Mechanical ventilator support         61 (39.6%)           Ionotropic support         43 (27.9%)           Length of first hospital stay (Days)         Minimum           Maximum         36           Median(IQR)         12 days (4-15)           Outcome         Survivors         132 (85.7)	Bulging fontanels	14 (9)
Neck stiffness         43 (27.9)           Kerning's sign         22 (14.3)           Brudzincski's sign         29(18.8)           Dilated poorly reactive pupils         4 (2.6)           GCS at presentation         109 (70.8)           Less than eight         45 (29.2)           Complications         127 (82.5)           Convulsions         99 (64.2)           Shock         56 (36.4)           Mechanical ventilator support         61 (39.6%)           Ionotropic support         43 (27.9%)           Length of first hospital stay (Days)         Minimum           Maximum         36           Median(IQR)         12 days (4-15)           Outcome         Survivors         132 (85.7)	Focal neurological signs	11 (7.1)
Brudzincski's sign 29(18.8)  Dilated poorly reactive pupils 4 (2.6)  GCS at presentation  More than thirteen 109 (70.8)  Less than eight 45 (29.2)  Complications  Altered level of consciousness 127 (82.5)  Convulsions 99 (64.2)  Shock 56 (36.4)  Mechanical ventilator support 61 (39.6%)  Ionotropic support 43 (27.9%)  Length of first hospital stay (Days)  Minimum 1  Maximum 36  Median(IQR) 12 days (4-15)  Outcome		43 (27.9)
Dilated poorly reactive pupils 4 (2.6)  GCS at presentation  More than thirteen 109 (70.8)  Less than eight 45 (29.2)  Complications  Altered level of consciousness 127 (82.5)  Convulsions 99 (64.2)  Shock 56 (36.4)  Mechanical ventilator support 61 (39.6%)  Ionotropic support 43 (27.9%)  Length of first hospital stay (Days)  Minimum 1  Maximum 36  Median(IQR) 12 days (4-15)  Outcome  Survivors 132 (85.7)	Kerning's sign	22 (14.3)
More than thirteen   109 (70.8)	Brudzincski's sign	29(18.8)
More than thirteen   109 (70.8)	Dilated poorly reactive pupils	4 (2.6)
Less than eight 45 (29.2)  Complications  Altered level of consciousness 127 (82.5)  Convulsions 99 (64.2)  Shock 56 (36.4)  Mechanical ventilator support 61 (39.6%)  Ionotropic support 43 (27.9%)  Length of first hospital stay (Days)  Minimum 1  Maximum 36  Median(IQR) 12 days (4-15)  Outcome  Survivors 132 (85.7)	GCS at presentation	
Complications	More than thirteen	109 (70.8)
Altered level of consciousness 127 (82.5)  Convulsions 99 (64.2)  Shock 56 (36.4)  Mechanical ventilator support 61 (39.6%)  Ionotropic support 43 (27.9%)  Length of first hospital stay (Days)  Minimum 1  Maximum 36  Median(IQR) 12 days (4-15)  Outcome  Survivors 132 (85.7)	Less than eight	45 (29.2)
Convulsions   99 (64.2)     Shock   56 (36.4)     Mechanical ventilator support   61 (39.6%)     Ionotropic support   43 (27.9%)     Length of first hospital stay (Days)     Minimum   1     Maximum   36     Median(IQR)   12 days (4-15)     Outcome   Survivors   132 (85.7)	Complications	
Shock   56 (36.4)     Mechanical ventilator support   61 (39.6%)     Ionotropic support   43 (27.9%)     Length of first hospital stay (Days)     Minimum   1     Maximum   36     Median(IQR)   12 days (4-15)     Outcome   Survivors   132 (85.7)	Altered level of consciousness	127 (82.5)
Mechanical ventilator support  Ionotropic support  Length of first hospital stay (Days)  Minimum  Maximum  Maximum  Median(IQR)  Outcome  Survivors  Survivors  Minimum  1  Maximum  12  Maximum  136  Median(IQR)  Survivors  Median(IQR)  Survivors  132 (85.7)	Convulsions	99 (64.2)
Ionotropic support Length of first hospital stay (Days)  Minimum Maximum Maximum Median(IQR) Median(IQR) Survivors  Survivors  Minimum 1  Maximum 1  Maximum 36  Median(IQR) 12 days (4-15)	Shock	56 (36.4)
Length of first hospital stay (Days)  Minimum 1  Maximum 36  Median(IQR) 12 days (4-15)  Outcome  Survivors 132 (85.7)	Mechanical ventilator support	61 (39.6%)
Minimum   1     Maximum   36     Median(IQR)   12 days (4-15)   Outcome   Survivors   132 (85.7)	Ionotropic support	43 (27.9%)
Maximum   36		
Median(IQR) 12 days (4-15)  Outcome  Survivors 132 (85.7)	Minimum	1
Outcome Survivors 132 (85.7)	Maximum	36
Survivors 132 (85.7)	Median(IQR)	12 days (4-15)
	Outcome	
Evnired 22 (14 204)	Survivors	
Explica   22 (14.370)	Expired	22 (14.3%)

# Discussion

Meningitis is a serious medical emergency. It is a life-threatening infectious disease associated with fatal complications. The recent medical literature reveals that it is prevalent globally but its prevalence is much high in tropical countries <sup>10</sup>. In highly developed countries the incidence rate is quite low, this can be attributed to vaccination of children population against this contagious disease <sup>11</sup>. However, in the developing countries like Pakistan, we still observe a huge burden of ailment caused by meningitis <sup>12</sup>. A study conducted by a collaboration of WHO recommends that in suspected cases of meningitis belonging to developing tropical countries, culture should be obtained and empirical antimicrobial therapy should be started without any delay. The diagnosis of



meningitis is confirmed by CSF culture. This is the "gold standard" for the establishment of the diagnosis of meningitis<sup>13</sup>. Furthermore, it rationalizes the management plan. Therefore, the specific antibiotic treatment for bacterial meningitis is of supreme importance. Unfortunately, it takes a considerable amount of time as it relies on the identification of causative agent. Most common organisms are streptococci, Neisseria meningitides, Haemophilus influenza type b and pneumococci <sup>14</sup>. Thus, the antimicrobial sensitivity data among the CNS infections is important to effectively manage meningitis patients in the first critical hours of treatment. Conversely, we observed that this is a most neglected aspect of the disease. A study by Amna J et al reports that cerebrospinal fluid culture was not done in 67% patients with meningitis <sup>15</sup>. This situation depicts that our junior resident doctors are not following the standard operative principles of disease management. This situation results in abuse of broad-spectrum antimicrobial drugs on hit and trial basis. The authors are of the view that this malpractice will culminate in severe resistance against most of the widely used broad-spectrum antibiotics.

The results of present study exposed that the age of study population ranged from 1 month to 12 years and seventy-five percent of them were below 5 years. This finding is consistent with the results of a study conducted at Aga Khan University Hospital, Karachi, in which the frequency of children having age less than five years was 67 % 15. In our study the female gender show preponderance towards the development of disease, it is in contrast to the study by Farag H et al. This Egyptian study by Frag et al revealed that the male was a predominant population of their study<sup>16</sup>. Our study also found that most of the patient belonged to rural areas (n=127, 82.4%). This finding can be co-related with the fact that in most of the rural areas of developing countries like Pakistan, a huge number of children remain un-vaccinated<sup>17</sup>. So the high incidence of meningitis can be associated with the vaccination failure or the lack of vaccination against the common causative agents of meningitis. In a study conducted at Department of Pediatric Medicine, Queen Mamohato Memorial Hospital, Maseru, Roma, the acute bacterial meningitis was the most frequent diagnosis (55%), followed by Viral (23%) and cryptococcal meningitis (15%) 11. The results of this study by Thinyane H et al are very close to the findings of our study. However, in the above mentioned European study, the percentage of tuberculous meningitis was surprisingly low as compared to our study. This high incidence of tuberculous meningitis in our study can be attributed to the high prevalence of TB in Pakistan. But further studies are required to explore this aspect in a focused way. In another study of Pakistani children population, the common clinical manifestations or the presenting complaints were fever 85.8%, vomiting 48.4%, headache 40.1%, irritability 28.1%, fits 24.5% and drowsiness 13.5%. These observations are highly coherent with the result of our study <sup>18</sup>. However, the mortality rate was quite high in our study (14.3%) in contrast to the studies conducted at highly well equipped and resource-rich centers of America and Europe 19,20

## Conclusion

Meningitis is a highly morbific and fatal central nervous system infection in children population. It is associated with life-threatening complications and exhibits highly diverse clinical course with a very non-specific sign and symptoms. Younger children of rural areas are highly prone to fall a victim to this lethal disease. By vaccinating the children population against causative agents of meningitis we can significantly reduce the burden of the disease.

# Reference

- 1. Martin NG, Sadarangani M, Pollard AJ, Goldacre MJ. Hospital admission rates for meningitis and septicemia caused by Haemophilus influenzae, Neisseria meningitides, and Streptococcus pneumoniae in children in England over five decades: a population-based observational study. *The Lancet Infectious Diseases*. 2014;14(5):397-405.
- 2. Boos C, Daneshvar C, Hinton A, Dawes M. An unusual case of chronic meningitis. *BMC family practice*. 2004;5(1):21.
- 3. Davison K, Ramsay M. The epidemiology of acute meningitis in children in England and Wales. *Archives of disease in childhood.* 2003;88(8):662-664.
- 4. Başpınar EÖ, Dayan S, Bekçibaşı M, et al. Comparison of culture and PCR methods in the diagnosis of bacterial meningitis. *brazilian journal of microbiology*. 2017;48(2):232-236.
- 5. Taylor WR, Nguyen K, Nguyen D, et al. The spectrum of central nervous system infections in an adult referral hospital in Hanoi, Vietnam. *PLoS One.* 2012;7(8):e42099.
- 6. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *New England journal of medicine*. 1997;337(14):970-976.
- 7. Sutinen J, Sombrero L, Paladin FJE, et al. Etiology of central nervous system infections in the Philippines and the role of serum C-reactive protein in excluding acute bacterial meningitis. *International journal of infectious diseases.* 1999;3(2):88-93.
- 8. Fernandez M, Moylett EH, Noyola DE, Baker CJ. Candidal meningitis in neonates: a 10-year review. *Clinical infectious diseases.* 2000;31(2):458-463.



- 9. Hay S. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. 2017.
- 10. Tan JL, Nordin S, Besari A. Rare Clinical Presentation of Tuberculous Meningitis: A Case Report. *Malaysian Journal of Medical Sciences*. 2017;24(5).
- 11. Thinyane KH, Motsemme KM, Cooper VJL. Clinical presentation, etiology, and outcomes of meningitis in a setting of high HIV and TB Prevalence. *Journal of tropical medicine*. 2015;2015.
- 12. Kulik DM, Uleryk EM, Maguire JL. Does this child have bacterial meningitis? A systematic review of clinical prediction rules for children with suspected bacterial meningitis. *Journal of Emergency Medicine*. 2013;45(4):508-519.
- 13. Tian R, Hao S, Hou Z, Gao Z, Liu B. The characteristics of post-neurosurgical bacterial meningitis in elective neurosurgery in 2012: A single institute study. *Clinical neurology and neurosurgery*. 2015;139:41-45.
- 14. Jiang H, Su M, Kui L, et al. Prevalence and antibiotic resistance profiles of cerebrospinal fluid pathogens in children with acute bacterial meningitis in Yunnan province, China, 2012-2015. *PloS one*. 2017;12(6):e0180161.
- 15. Jawaid A, Bano S, Haque A, Arif K. Frequency and outcome of meningitis in Pediatric Intensive Care Unit of Pakistan. *Journal of College of Physicians and Surgeons Pakistan*. 2016;26(8):716.
- 16. Farag HM, Abdel-Fattah M, Youssri A. Epidemiological, the clinical and prognostic profile of acute bacterial meningitis among children in Alexandria, Egypt. *Indian Journal of Medical Microbiology*. 2005;23(2):95.
- 17. Vonasek BJ, Bajunirwe F, Jacobson LE, et al. Do maternal knowledge and attitudes towards childhood immunizations in rural Uganda correlate with complete childhood vaccination? *PloS one*. 2016;11(2):e0150131.
- 18. Fayyaz J, Rehman A, Hamid A, Khursheed M, Zia N, Feroze A. Age-related clinical manifestation of acute bacterial meningitis in children. *Journal of Pakistan Medical Association*. 2014;64(3):296.
- 19. Boyles TH, Bamford C, Bateman K, et al. Guidelines for the management of acute meningitis in children and adults in South Africa. *Southern African Journal of Epidemiology and Infection*. 2013;28(1):5-15.
- 20. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *New England Journal of Medicine*. 2011;364(21):2016-2025.