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1 Prospective surveillance of drain-associated meningitis / ventriculitis in a neurosurgery and a
2 neurologic intensive care unit.

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5 Running title: Surveillance of drain-associated meningitis

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24

25 **Abstract:**

26 **Objectives - There are currently no data available on drain-associated infection occurrence**
27 **related to the number of drainage-days, and thus drain-associated infection rates.**

28 **Therefore, we conducted a prospective surveillance study to determine drain-associated**
29 **infection rates and drainage-days of hospital-acquired external ventricular drain- (EVD)**
30 **and lumbar drain- (LD) associated meningitis/ventriculitis in a neurosurgery (NSICU) and a**
31 **neurologic intensive care unit (NICU).**

32 **Methods - All patients admitted in 2005 and 2006 were documented. Data on age, admitting**
33 **diagnosis, type and duration of drain, duration of hospital stay and occurrence of meningitis**
34 **were recorded and analysed statistically.**

35 **Results – A total of 1333 patients were included amounting to 3023 drainage days (DD).**

36 **After exclusion of 15 contaminations, a total of 26 cases of meningitis were reported**
37 **accounting for an overall device-associated meningitis rate of 8.6 infections/1000 DD.**

38 **Infections associated with LD seemed to occur more frequently (19.9/1000 DD) compared to**
39 **EVD (6.3/1000 DD). The presence of intraventricular blood and previous trauma were**
40 **significant risk factors for infection (p=0.003; p=0.04). Finally, the length of stay was**
41 **significantly longer in meningitis patients (p=0.0003). Coagulase negative staphylococci**
42 **(CoNS) were the main pathogen (56%) causing meningitis followed by S. aureus (25%).**

43 **Conclusions - To the best of our knowledge, this study represents the first to provide data on**
44 **EVD- as well as LD-associated meningitis rates calculated per 1000 DD; a parameter that is**
45 **well established for other invasive devices such as central venous and urinary tract**
46 **catheters. However, further prospective studies are needed to investigate possible risk**
47 **factors for meningitis.**

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52 **INTRODUCTION**

53 Nosocomial infection rates mainly correspond with the severity of illness and the exposure to
54 invasive devices [1]. External ventricular drains (EVD) and lumbar drains (LD) are commonly
55 used to control hydrocephalus and to monitor and decrease intracranial pressure.

56 Ventriculostomy-related infections are a serious problem in up to 40% of patients [2-5]. In
57 contrast to shunt infections, infections derived from the use of devices are almost always
58 classified as nosocomial due to the requirement of hospitalization [6, 7]. To date, there have been
59 studies on the incidence (IR) of meningitis, causative organisms and drain-specific data in both
60 the neurosurgical and the neurological setting [8-11]. However, there have been no studies
61 correlating meningitis with drain-specific device-days (DD), and therefore, there are no data on
62 drain-associated incidence rates (DA-IR) relating meningitis to drainage-days (DD).

63 The definition of drain-associated meningitis is still not clearly defined and open to discussion in
64 the literature [12]. This may therefore lead to infection rates being overestimated when using the
65 CDC definition due to defining contaminations as infections. The aim of this study was to test the
66 suitability of the CDC definition for drainage-associated meningitis and to identify the possible
67 underlying risk factors for meningitis cases by determining utilization rates (UR) and drain-
68 associated meningitis rates (DA-IR).

69

70 **METHODS**

71 **Study wards and patients**

72 The study was performed prospectively from 1 January 2005 to 31 December 2006. The
73 neurosurgical ICU (NSICU) is a fourteen-bed ward and the neurological ICU (NICU) is a
74 seven-bed ward; both care for adult patients only. To determine the total number of patients
75 and patient-days, only patients who stayed longer than 24 hours were included. Each EVD
76 and LD was counted separately to calculate the number of EVD- as well as LD-days, and the
77 duration of drainage was documented for all patients in the NICU throughout the study and for the
78 patients in the NSICU for 2006.

79 LD and EVDs were routinely inserted under sterile conditions at the patient`s bedside, and seldom
80 (<5%) in the operating theatre. The "Portex Epidural Catheter" and "Liquor Drainage Catheter
81 Set" (both Smiths Medical, Kirchseeon, Germany) were used for EVD and LD, respectively.
82 Note that neither antibiotic nor silver-impregnated catheters were used. A written protocol was
83 followed for drainage placement, and the preferred insertion point of the EVD was the Kocher
84 point on the right side with no tunnelling being carried out. No antibiotics were given
85 prophylactically and no prophylactic catheter changes were performed. EVD- and LD-related
86 infections were recorded only when the patients were admitted for longer than 48 hours.
87 When infection was suspected, white cell count, protein and glucose levels for cerebrospinal
88 fluid (CSF) and C-reactive protein serum levels (CRP), total white blood cell counts (WBC)
89 as well as microbiologic examination were performed daily. Otherwise tests were routinely
90 carried out 3-4 times a week. CSF sampling was carried out by aseptic techniques following a
91 written protocol by the neurosurgeon or the neurologist. Microbiological examination was
92 performed using conventional culture techniques as well as the BD Phoenix automated
93 microbiology system (Becton Dickinson Diagnostic Systems, Heidelberg, Germany).
94 Admitting diagnoses of patients needing drainage therapy were SAH (55%), ICB (24%),
95 SAH+ICB (4%), neoplasm (6%), infection (3%), and others (8%). In 7.5%, bleedings followed
96 trauma. Since no differences were found for the admitting diagnoses and surgical interventions for
97 the NSICU and NICU patients, data were pooled for patients with meningitis.

98

99 **Surveillance and data collection**

100 Surveillance was performed by an experienced infection control team and instructed staff
101 members using a nursing documentation sheet and mid-night statistics. The following parameters
102 were collected: sex, age, admitting diagnosis, surgical procedures, type of drainage, clinical signs
103 indicative for meningitis / ventriculitis, parameters to determine inflammation from the serum and
104 CSF, causative organism and frequency of isolation, resistance pattern, and initiation of

105 antibiotics for the reason of meningitis/ventriculitis. Firstly, each detection of a pathogen in the
106 CSF and / or at the tip of the drain was documented as meningitis / ventriculitis according to the
107 CDC definition. Moreover, the combination of at least one typical clinical sign indicating
108 meningitis (e.g neck stiffness), at least one pathologic parameter in the CSF (elevated cell count,
109 decreased glucose level in our cases) and the initiation of antibiotics due to suspicion of
110 meningitis as defined by the CDC (second criterion of the case definition). Secondly,
111 contaminations were excluded after investigation of these cases suspicious for contamination only
112 according to the criteria derived from our results. Finally, meningitis cases were excluded if
113 meningitis followed a systemic infection (e.g. central venous line sepsis).
114 For correlation of meningitis with drainage-day, admitting diagnosis, age data were available for
115 all NICU patients cared with drainage and for all NSICU patients with drainage admitted during
116 2006. Student's t-test (level of significance $p < 0.05$; CI 95%) and Chi-square test were used to
117 calculate means, differences, and odds ratios.

118

119 **RESULTS**

120 **Microbiology**

121 In 40 nosocomial drain-associated cases of meningitis, a pathogen was isolated. In four patients,
122 more than one episode of ventriculitis with different pathogens was detected. In general,
123 *Coagulase negative staphylococci* (CoNS) was found to be the main pathogen, followed by
124 *Staphylococcus aureus* (SA). Blood stream infection was found to occur in only one case after
125 meningitis (due to SA). Interestingly, in four EVD-/LD-associated infections, methicillin-resistant
126 SA (MRSA; 10%) was isolated accounting for an MRSA rate of 57% (4/7) for all cases of *S.*
127 *aureus*- induced meningitis. Finally, two-thirds of CoNS were found to be oxacillin resistant,
128 whereas none of the other pathogens showed any unusual antibiotic-resistance pattern. Data on
129 species, frequency of the isolated organism, relation to the device and fulfilling the CDC case
130 definition are provided in table 1.

131

Causative organism	EVD	LD	Σ (%)	Criterion 1 only (%)	Criterion 1+2 (%)
Σ (CoNS)	13	16	29 (73)	25 (86)	4 (14)
Σ (<i>S. aureus</i>), divided into	3	4	7 (18)	3 (43)	4 (57)
• <i>S. aureus</i> , MSSA	2	1	3 (8)	2 (67)	1 (33)
• <i>S. aureus</i> , MRSA	1	3	4 (10)	1 (25)	3 (75)
<i>Enterococcus faecalis</i>	1	0	1 (2.5)	0 (0)	1(100)
<i>Acinetobacter baumannii</i>	1	0	1 (2.5)	0 (0)	1 (100)
<i>Pseudomonas aeruginosa</i>	1	0	1 (2.5)	0 (0)	1(100)
<i>Candida albicans</i>	1	0	1 (2.5)	0 (0)	1(100)
Σ (all microorganism)	20	20	40	28 (70)	12 (30)

132 Table 1: Causative organisms and diagnosis of infection according to the CDC definition

133 Legend of Table 1: Criterion 1: detection of a microorganism in CSF

134 Criterion 2: at least one clinical symptom + at least one positive
135 laboratory result + starting of antimicrobial therapy

136

137 Definition of meningitis

138 Patients diagnosed with meningitis from CSF analysis did not often comply with the second
139 criterion of the CDC definition, especially when it was CoNS-induced. For example, only in 13 of
140 41 patients (32%), could clinical signs be described. A decreased glucose level in CSF was
141 detected in 15 of the 41 (37 %) meningitis patients and was found in all cases of meningitis due to
142 *S. aureus*, *E. faecalis*, Gram-negative rods and yeasts. In contrast, in 90% (37/41) of our patients,
143 WCC were elevated in the CSF and ranged from 16 and 4270 with an average of 868 cells / ml
144 CSF specimen. Of note was that more than 90% of analysed CSF specimens were at least
145 moderately bloody (++) and more than 50% were highly blood stained (++++). In 22 of 41 cases
146 (54%), patients were prescribed antibiotics against a possible meningitis.

147 To ascertain whether the frequency of isolating CoNS allows us to distinguish true infections
148 from contaminations we subdivided the patients with regard to the number of positive CSF results
149 Only cases in which a positive CSF specimen was followed by at least one negative one were
150 documented as 'isolation once'. We found that isolating CoNS twice or more seemed to be

151 indicative of meningitis infection, whereas isolating CoNS in only one sample seemed to be
 152 indicative of contamination only (see table 2).

CoNS	Isolation once (N=15) (%)	Isolation twice or more (N=10) (%)
CDC definition:		
Criterion 1 only	15 (100)	6 (60)
Criterion 1+2	0 (0)	4 (40)
LD	9 (60)	4 (40)
EVD	6 (40)	6 (60)
Symptomatic +	0 (0)	4 (40)
WBC CSF (M/μl)	341	1064
Glc level CSF (mg/dl)	65	64
Protein CSF (mg/dl)	0.8	0.7
Antibiotic therapy +	3 (20)	7 (70)

153 Table 2: Frequency of isolating CoNS in correlation to diagnostic criteria

154

155 **Device utilization and nosocomial infection rates**

156 During the two-year prospective surveillance study, a total of 1333 (NSICU: N = 746; NICU: N =
 157 587) patients (P) were enrolled accounting for a total of 11822 (NSICU: N = 7046; NICU: N =
 158 4776) patient-days (PD). A total of 3023 drainage-days (DD) were observed of which 503 were
 159 LD-days (LD-D) and 2520 EVD-days (ED-D). The majority of catheters were used on the NSICU
 160 with 2732 DD, accounting for 2267 ED-D and 465 LD-D. On the NICU, a total of 291 DD were
 161 counted of which 253 were ED-D and 28 LD-D. 37 out of 1333 patients accounted for 41
 162 episodes of nosocomial device-associated meningitis / ventriculitis with 37 and 4 infections
 163 occurring in the NSICU and NICU, respectively. Results for the device utilization rate (UR), the
 164 incidence rate (IR) of meningitis / ventriculitis (calculated per 100 patients = 100 P), the incidence
 165 densities (ID) and the device-associated meningitis / ventriculitis rates (DA-IR, calculated per
 166 drainage-days) as well as the formulas used to derive the results are provided in table 3. Exclusion
 167 of the cases with contaminants only resulted in considerably Seite: 7

168 lower overall DA-IR (8.6 versus 13.6 infections per 1000 drainage-days; EVD: 6.3 versus 8.7
 169 infections per 1000 drainage-days; LD: 19.9 versus 37.8 infections per 1000 drainage-days).

	DUR: <u>DD x 100</u> PD	IR: <u>DAI</u> 100 P	ID: <u>DAI x 1000</u> PD	DA-IR: <u>DAI x 1000</u> DD
LD(NSICU)	6.6	1.3	1.4	21.5
EVD(NSICU)	32.2	1.7	1.8	5.7
Σ (NSICU)	38.8	3.1	3.3	8.4
LD(NICU)	0.8	0.0	0.0	0.0
EVD(NICU)	5.3	0.5	0.6	11.9
Σ (NICU)	6.1	0.5	0.6	10.3
Σ (LD)	4.3	0.8	0.8	19.9
Σ (EVD)	21.3	1.2	1.1	6.3
Σ	25.6	2.0	2.2	8.6

170 Table 3: Formulas for calculation and the derived results

171 Legend for Table1:

172 DAI: device-associated infections; DA-IR: device-associated infection rate (calculated per device-days);

173 DD: device-day; ID: incidence-density; IR: incidence rate;urgical ICU; P: patient; PD: patient-day

174

175 **Characterization of meningitis and meningitis patients:**

176 The mean age of patients having had meningitis was 49.09 years (SD: 12.75; range: 26-77) and no
 177 difference to drainage-patients without infection was found (53.47 years, SD: 15.35; range: 15-85;
 178 p=0.20). The mean length of hospital stay was 34.70 (SD: 19.18; range: 4-113) days for patients
 179 with drain and without meningitis compared to 51.46 (SD: 26.64; range: 7-114) days for
 180 meningitis patients. The differences between patients without and with infection were statistically
 181 significant (p =0.0003) and for EVD were 34.48 days (SD: 20.82) without infection versus 55.56
 182 days (SD: 25.38) with infection (p= 0.0006). The mortality in the meningitis group (3/26, in one
 183 case due to infection) did not differ significantly from the mortality in patients with drains and
 184 without meningitis (OR: 1.34, CI 95: 0.35-5.05; p=0.67).

185 Meningitis occurred more often in patients with LD than EVD (Table 1); however, the difference
 186 was not statistically significant (Table 4). Association of admitting diagnosis with infection was
 187 seen only for trauma previous to bleeding. Detection of intraventricular blood by CCT was
 188 significantly correlated with meningitis (Table 4).

189

Meningitis	OR (CI 95%)	p (<0.05)
LD versus EVD	1.39 (0.58-3.30)	0.46
Previous trauma	3.21 (1.00-10.33)	0.04
Intraventricular blood (CCT; NSICU)	4.93 (1.57-15.45)	0.003
LD placement >9 days	1.38 (0.29-6.48)	0.68
EVD placement > 9 days	0.61 (0.25-1.48)	0.27

190 Table 4: Risk factors analysis for meningitis

191

192 The mean duration of drainage placement was 11.11 days (SD: 7.33; range: 1-35) for EVD in the
 193 noninfected patients and 12.56 days (SD: 9.02; range: 1-37) in meningitis patients with no
 194 significant difference (p=0.48). The mean duration of LD-placement in the non-infected patients
 195 was 6.92 days (SD: 4.91, range: 1-22) in contrast to 8.20 days (SD: 5.98; range: 3-23) in the
 196 meningitis group with no significant difference (p=0.49). However, the longer EVD placement
 197 differed significantly from the LD duration (p=0.0003).

198 Drainage duration of more than 9 days did not correlate with meningitis infection in our group.

199 For correlation of the occurrence of meningitis and the drainage day – before and after excluding
 200 contaminations – see Figure 1.

201

202 **DISCUSSION**

203 The literature on surveillance data about nosocomial infections, knowledge about the
 204 pathophysiology as well as risk factors is steadily increasing [13, 14]. However, despite there
 205 being many studies on and subsequently guidelines about preventing infections, especially those
 206 that are device-associated, drain-related infection occurrence and number of drainage-days, and
 207 thus drain-related infection rates are lacking [15-17], thereby severely hampering meaningful

208 comparison and benchmarking and the development of effective disease prevention
209 guidelines/measures. Intraventricular haemorrhage (IVH) was previously identified as a risk
210 factor for meningitis with reported IR in up to 37.5/100P [2, 3, 18]. Therefore, patients in this
211 study have to be classified as a high risk group and IVH was also identified to correlate with
212 meningitis. In our study, we obtained a mean device-associated incidence rate (DA-IR) of 8.6
213 infections per 1000 drainage-days after eliminating contaminants, which to our knowledge
214 represent the first reported DA-IRs calculated per DD. DA-IRs per DD can be used as a
215 surveillance parameter and is well established for other device-associated infections, e.g. central-
216 line associated blood stream infection, and is accepted to represent the most stable and valid
217 parameter for these device-associated infections [19].
218 However, there are difficulties in comparing published data, especially the surveillance parameter.
219 For example, some investigators document the overall, not only device-associated infections, and
220 in some studies, data on meningitis and ventriculitis are presented separately [8, 10], while others
221 are divided into LD- and EVD-associated meningitis. For example, Schade et al. (2005 and 2006
222 [15, 16]) calculated an IR of 7/100 P with LD and 15/100 P with EVD and Orsi et al. (2006)
223 obtained IR of 3/100 P with LD or EVD [17]. A basic difference is due to comparison of
224 infections in 100 patients by some [8, 10] and in 100 patients with drainage by others [15-17].
225 Moreover, mainly IR and ID (calculation per 100 P or per PDs) are given, but DA-IR calculated
226 per device-days (DA-IR) are not [4, 5, 8, 10, 12, 20-25]. Calculating the incidence rate (IR) per
227 100 patients in our group with an IR of 3.08/ 100 pts (0.7 in NICU and 5.0 in NSICU) fall within
228 the broad range of published data on meningitis associated with shunt or drain [11, 12, 15-17, 20-
229 28]. In other studies where the device-days were taken into account, the infections were related to
230 the number of device kits or procedures, but not to device-days [11, 22]. For example, Coplin and
231 coworkers calculated the LD-associated IR to be 4.2% related to kits [22]. In comparison to our
232 results, Dettenkofer et al. reported slightly lower IRs in the NICU (1.2/100 P) than in the NSICU
233 (1.8/100 P) [1, 3]. However, this apparent discrepancy in our study population was not confirmed
234 when comparing DA-IR (NICU: 10.3; NSICU: 8.4 infections per 1000 drainage-days). Thus, the

235 difference seems only to be simulated due to the varying UR for both ICUs. In contrast, the risk of
236 infection seems to be higher for LD with a DA-IR of 19.9 infections per 1000 drainage-days than
237 for EVD with a DA-IR of 6.3 infections per 1000 drainage-days in our study. There is no obvious
238 explanation for this finding, and thus, further studies are needed. To summarize, DA-IRs
239 calculated per device-days is accepted to represent the most stable and valid parameter, that can
240 be used as a benchmark to help develop effective preventative measures, thereby lowering the
241 level of infection and improving patient outcome. Finding CoNS to be the most frequent pathogen
242 of drain-associated meningitis (56%) was not surprising [2, 29]. Data published on shunt
243 infections showed staphylococcal species to be the cause of at least 60% of infections and mainly
244 due to CoNS, followed by Gram-negative rods found in up to 20% of cases [8, 12, 20, 22, 25, 30,
245 31]. It is standard practice to follow the CDC definitions for which every detected microorganism
246 has to be evaluated as a potential causative organism [2, 8, 10, 17, 29]. However, some
247 investigators only included bacteriologically proven infections [22, 24], and others excluded cases
248 when CoNS and other skin commensals like *Corynebacterium ssp.* were isolated by using the
249 investigators own definitions and in these case, they were classified as contaminants or
250 colonization of the catheter only [16, 32]. However, care must be taken not to oversimplify
251 possible causative organisms such as CoNS and other factors, e.g. frequency of isolation should
252 also be taken into consideration to help make a more accurate diagnosis in the cases of CoNS [5,
253 8, 12, 16, 20-25]. Of note is that studies on shunt infections have already shown that the absence
254 of fever and indicators of meningitis does not rule out the possibility of meningitis infection [17,
255 33]. This finding is partly to be expected when one considers the low virulence of CoNS
256 compared to, e.g. *S. aureus*. A non-specific and unsuspecting presentation of drain-associated
257 meningitis makes a rapid and appropriate diagnosis difficult. Moreover, pathological CSF
258 parameters also have to be interpreted with caution since patients with shunts or drainages often
259 show abnormal CSF profiles regardless of infection [17, 33]. There is also no clear cut-off value
260 on how to interpret elevated white cell counts by different degrees of blood-stained CSF although
261 patients with SAH or ICB have been reported to show elevated cell counts of more than 100/mm³

262 in the case of bacteriologically proven meningitis [22, 34]. In addition, whether the detection of
263 CoNS or other skin commensals in one single CSF specimen is sufficient to diagnose drain-
264 associated meningitis is questionable [20-22]. As known from the blood culture diagnosis, the
265 frequency of isolating CoNS is a well-established additional parameter to help between
266 discriminate contamination and infection [35]. Therefore, we investigated whether the frequency
267 of CSF samples with CoNS in our setting is of additional value in discriminating true meningitis
268 from contaminations only. None of our patients in whom CoNS was detected only once showed
269 clinical signs of meningitis. The misinterpretation of CoNS contaminants as indicative of true
270 infections has implications for both patient care and hospital quality assurance. Excluding the
271 cases diagnosed by isolating CoNS only once resulted in considerable lower device-associated
272 infection rates (8.6 versus 13.6 infections per 1000 drainage-days) in our patient group. The
273 modified case definition since January 2008 (National Reference Laboratory for the Surveillance
274 of Nosocomial Infections, Berlin, Germany) takes into consideration the possibility of
275 misinterpretation of contaminants [36]. Therefore, we would like to suggest the number of CSF
276 samples with isolation of CoNS as an additional criterion in discriminating true meningitis
277 infections from contaminations. We found that trauma bleeding after head injury and the presence
278 of intraventricular blood were significant risk factors for meningitis. In the presented study, we
279 found no obvious relationship between infection and drainage-day. Meningitis patients showed a
280 significantly longer duration of hospital stay than drainage-patient without meningitis. In addition
281 to our risk factor analysis, the techniques of drainage placement (e.g. tunnelling), the influence of
282 prophylactically-given antibiotics and the impact of the place where the insertion procedure was
283 carried out are of interest and should be evaluated in further studies.

284 In conclusion, to the best of our knowledge, we present the first IRs calculated in regard to
285 device- days for both EVD- and LD-associated meningitis / ventriculitis in a NSICU and NICU.
286 We would like to encourage the implementation of a routine surveillance program for both EVD-
287 and LD-associated meningitis / ventriculitis in hospitals caring for those patients. A significant

288 reduction of device-associated infections like central-line-associated blood stream infection could
289 be proven by generating these data [37].

290 Our findings show that risk factors for meningitis were the presence of intraventricular blood and
291 previous trauma. In addition, the length of hospital stay was significantly longer in patients with
292 meningitis. However, the commonly used definition of drain-associated meningitis / ventriculitis
293 [by the CDC; 38] may be of limited capacity to exclude true contaminants, thus resulting in an
294 overreporting of infections, especially overestimating the role of CoNS. Therefore, we would like
295 to suggest that the number of isolated CoNS be taken into account as an additional criterion to
296 rule out contaminants. Finally, further investigations are warranted in order to provide a more
297 effective framework for better diagnosing and analysing risk factors of infection to improve
298 patient outcome.

299

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308

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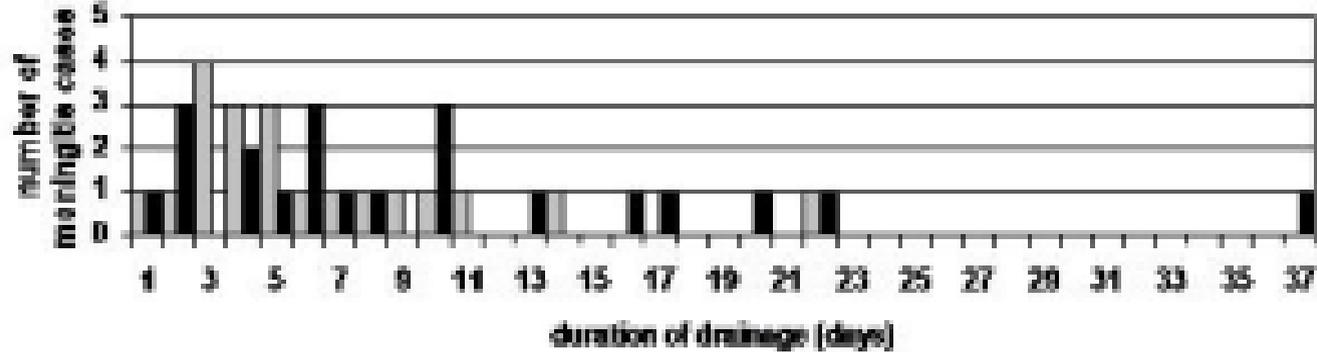
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406

Occurrence of meningitis related to the drainage-day

all "cases" (N=41)



after excluding contaminants (N=28)

