SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline characteristics of patients and controls.

Characteristic	Patients with DNA (n=439)	Controls (n=302)
Age (median- IQR[a])	59 (41-68)	58 (45-66)
Male sex	210 (48%)	148 (49%)
Ethnicity		
White	415 (94%)	287 (95%)
African	17 (4%)	13 (4%)
Asian	7 (2%)	2 (1%)

[a]IQR – interquartile range

Supplementary Table 2. Baseline characteristics of included patients with and without DNA.[a]

Characteristic	Patients with DNA (n=439)	Patients without DNA (n=197)	*P* value
Age	59 (41-68)	62 (49-72)	0.001
Male sex	210 (48%)	94 (48%)	0.430
Immunocompromise	96/436 (22%)	37/165 (20%)	0.915
Distant focus of infection	200/436 (46%)	73/165 (44%)	0.721
Clinical signs and symptoms			
Headache	340/394 (86%)	111/134 (83%)	0.327
Fever	326/396 (83%)	118/146 (81%)	0.687
Neck stiffness	325/421 (77%)	115/152 (76%)	0.528
Glasgow Coma Scale score[b]	11 (9-14)	10 (8-14)	0.039
Indices of cerebrospinal fluid inflammation[c]			
Leukocyte count - cells/mm^3	3232 (793-8675)	1700 (281-6538)	0.001
Glucose level – mmol/L	0.50 (0.00-2.60)	0.55 (0.20-2.21)	<0.001
Protein level – g/L	0.15 (0.00-1.40)	4.18 (2.49-6.05)	0.046
Causative microorganism			
S. pneumoniae	314 (72%)	150 (76 %)	0.867
N. meningitidis	63 (14%)	18 (9%)	0.363
Other	62 (14%)	29 (15%)	0.784
Mortality	35/435 (8%)	69/164 (42%)	<0.001
Unfavorable outcome	114/435 (25%)	98/164 (60%)	<0.001

[a] Data are number/number evaluated (percentage), continuous data are median (interquartile range) [b] Score on Glasgow Coma Scale was known in 434/439 (99%) patients with DNA and 162/197 (82%) patients without.[c] CSF leukocyte count was reported in 409/439 (93%) patients with DNA and 157/197 (80%) without, CSF glucose level was reported in 415/439 (95%) patients with DNA and 156/197 (79%) without, CSF protein level was reported in 412/439 (94%) patients with DNA and 154/197 (77%) without DNA.

Supplementary Table 3. Allele frequency, Hardy-Weinberg equilibrium and genotyping success rate of evaluated common complement component polymorphisms in 287 white controls.

Gen	SNP ID	A %	B %	A	B	AA	AB	BB	HWE[a] *P* - value	Success rate
C3	rs1047286	78,6%	21,4%	451	123	179	93	15	0,816	99,4%
C3	rs2230199	77,1%	22,9%	438	130	169	100	15	0,999	98,9%
C5	rs17611	43,2%	56,8%	247	325	53	141	92	0,997	99,7%
C6	rs1801033	69,3%	30,7%	398	176	138	122	27	1,000	99,3%
C7	rs1063499	35,2%	64,8%	202	372	40	122	125	0,514	99,6%
C7	rs13157656	23,0%	77,0%	129	433	13	103	165	0,831	97,7%
C7	rs60714178	16,4%	83,6%	94	480	8	78	201	0,991	99,9%
C8B	rs12067507	6,3%	93,7%	36	538	6	24	257	<0,001	99,6%
C8B	rs12085435	94,4%	5,6%	540	32	254	32	0	0,605	98,6%
C9	rs700233	61,7%	38,3%	343	213	106	131	41	0,999	95,7%
C9	rs34882957	94,3%	5,7%	532	32	250	32	0	0,600	98,7%
CFH	rs505102	70,4%	29,6%	404	170	143	118	26	0,973	99,3%
CFH	rs1065489	17,4%	82,6%	99	471	14	71	200	0,083	99,3%
CFH	rs1410996	54,9%	45,1%	315	259	83	149	55	0,715	99,7%
CFH	rs3753396	16,6%	83,4%	95	479	10	75	202	0,659	99,7%
CFH	rs6677604	80,5%	19,5%	459	111	187	85	13	0,710	99,1%
CFH	rs3753394	26,0%	74,0%	148	422	20	108	157	0,971	99,4%

[a]Hardy Weinberg equilibrium.

Supplementary Table 4. Multivariate logistic regression analysis for unfavorable outcome in pneumococcal meningitis.

Patient characteristic	**Odds ratio (95% confidence interval)**	***P* value**
Age	1.017 (0.996 – 1.039)	0.115
Glasgow coma scale score	1.152 (1.277 – 1.041)	0.006
Thrombocyte count	1.000 (0.997 – 1.003)	0.976
CSF leukocyte count <1000/mm^3	3.623 (1.976 – 6.623)	<0.001
Immunocompromise	1.686 (0.873 – 3.257)	0.120
Otitis/Sinusitis	0.513 (0.283 – 0.930)	0.028
Rs17611	1.920 (1.057 – 3.487)	0.032

Supplementary Table 5. Effects of different antibody treatment modalities on CSF leukocyte counts, clinical status, neuroscore, and cerebellar titers 24 hours after induction of pneumococcal meningitis

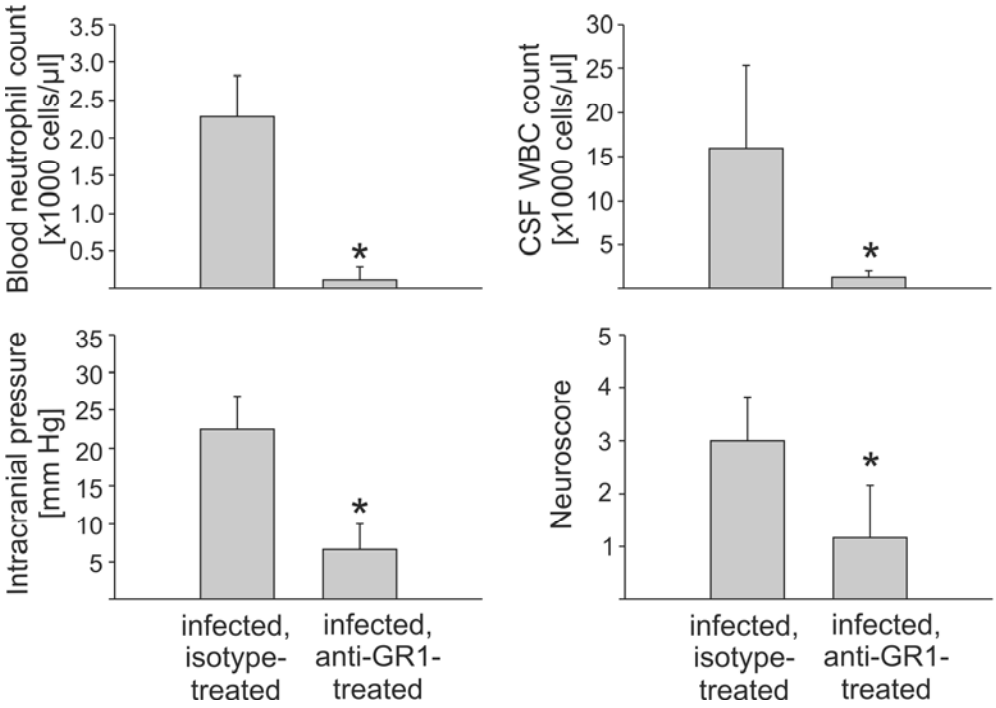
Antibody	**Route of administration**	**Dosage [µg/mouse]**	**Number of mice [n]**	**CSF WBC [cells/µl]**	**Clinical score**	**Neuroscore**	**Bacterial titer [log_{10} CFU/organ]**
Anti-CXCL2	i.p.	100	3	8,717 ± 1,537	5.00 ± 2.65	n.d.	6.49 ± 0.46
Isotype control (anti-CXCL2)	i.p.	100	3	14,600 ± 5370	6.33 ± 0.58	n.d.	6.42 ± 0.40
Anti-CXCL1/CXCL2	i.p.	100 each	4	5,338 ± 1,244*	3.75 ± 0.50*	n.d.	6.50 ± 0.37
Isotype controls (anti-CXCL1/2)	i.p.	100 each	4	14,367 ± 3,202	7.25 ± 1.71	n.d.	6.52 ± 0.52
Anti-C5	i.p.	30	3	15,917 ± 5,328	7,33 ± 1,53	n.d.	6.28 ± 0.44
Anti-C5	i.c.	30	4	6,388 ± 2,225*	3.50 ± 1.29*	n.d.	6.39 ± 0.25
IgG controls (anti-C5)	i.c.	30	4	14,275 ± 5,013	6.75 ± 1.71	n.d.	6.20 ±0.24
Anti-TLR2/4	i.p.	750 each	5	7,740 ± 3,583*	7.80 ± 0.84*	2.25 ± 0.69*	7.01 ± 0.32*
IgG controls (anti-TLR2/4)	i.p.	1500	5	15,200 ± 5,504	6.20 ± 0.45	4.00 ±1.22	6.03± 0.36

CSF = cerebrospinal fluid; WBC = white blood cell; CFU = colony forming units; i.p. = intraperitoneally; i.c. = intracisternally; n.d. = not determined.

* $p < 0.05$, compared to the respective control groups .

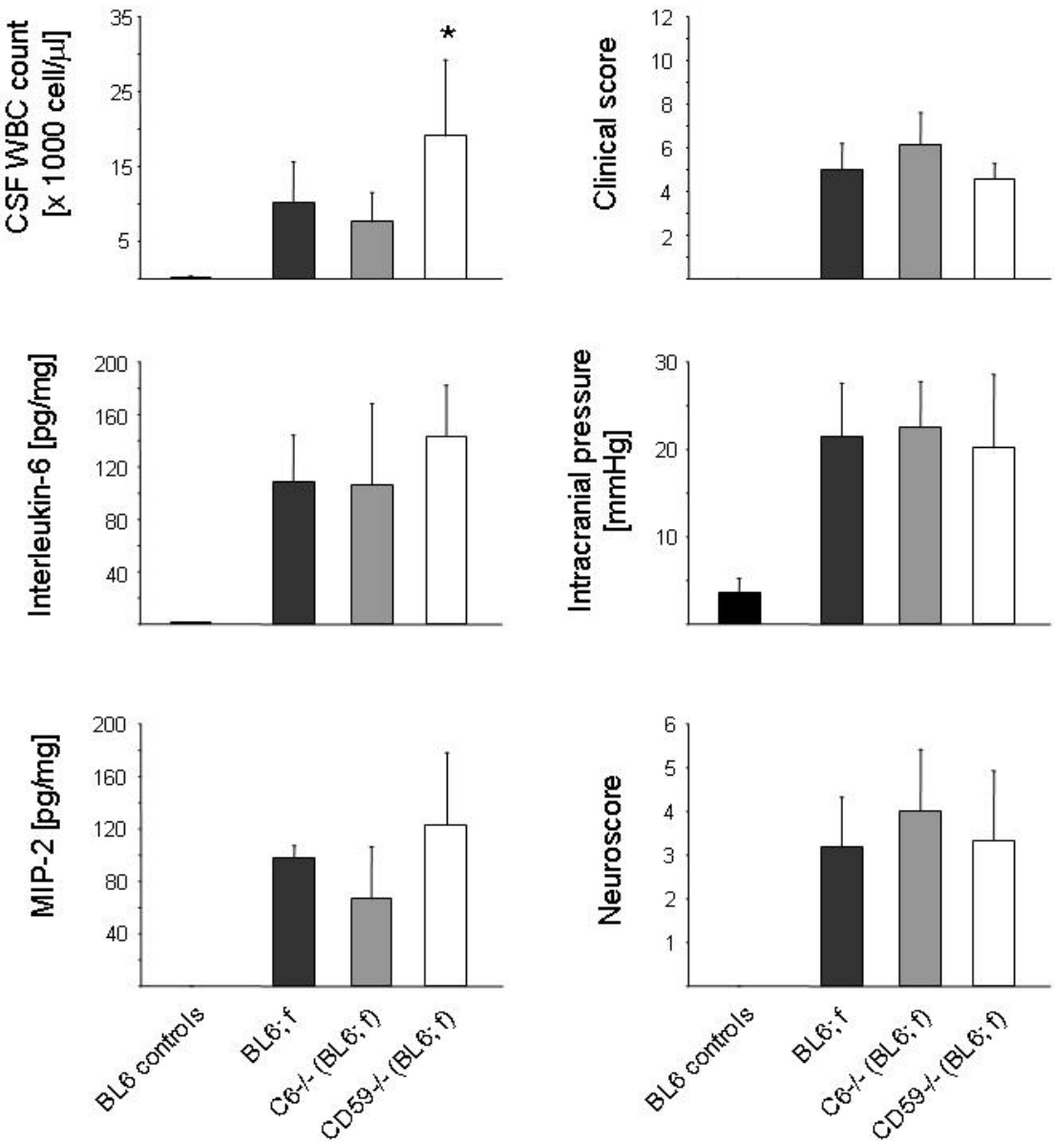
SUPPLEMENTARY FIGURES

Supplementary Figure 1: Effect of neutropenia in experimental pneumococcal meningitis.



In order to asses the role of neutrophils, wild type mice were treated with 250 µg of either anti-GR1-antibody or rat IgG2b isotype control antibody (n=8 per group) 24 hours before disease induction. Then, animals were infected with *S. pneumoniae* and evaluated 24 h later for blood neutrophil counts, CSF leukocyte counts (CSF WBC count), intracranial pressure (ICP), blood brain barrier-breaching and intracerebral hemorrhage combined in the neuroscore. Anti-GR1-treatment resulted in markedly lower blood neutrophil and CSF leukocyte numbers compared to isotype control-treated mice which was also paralleled by a significant reduction in ICP and neuroscore values (unpaired Student's test; data are shown as means ± SD).

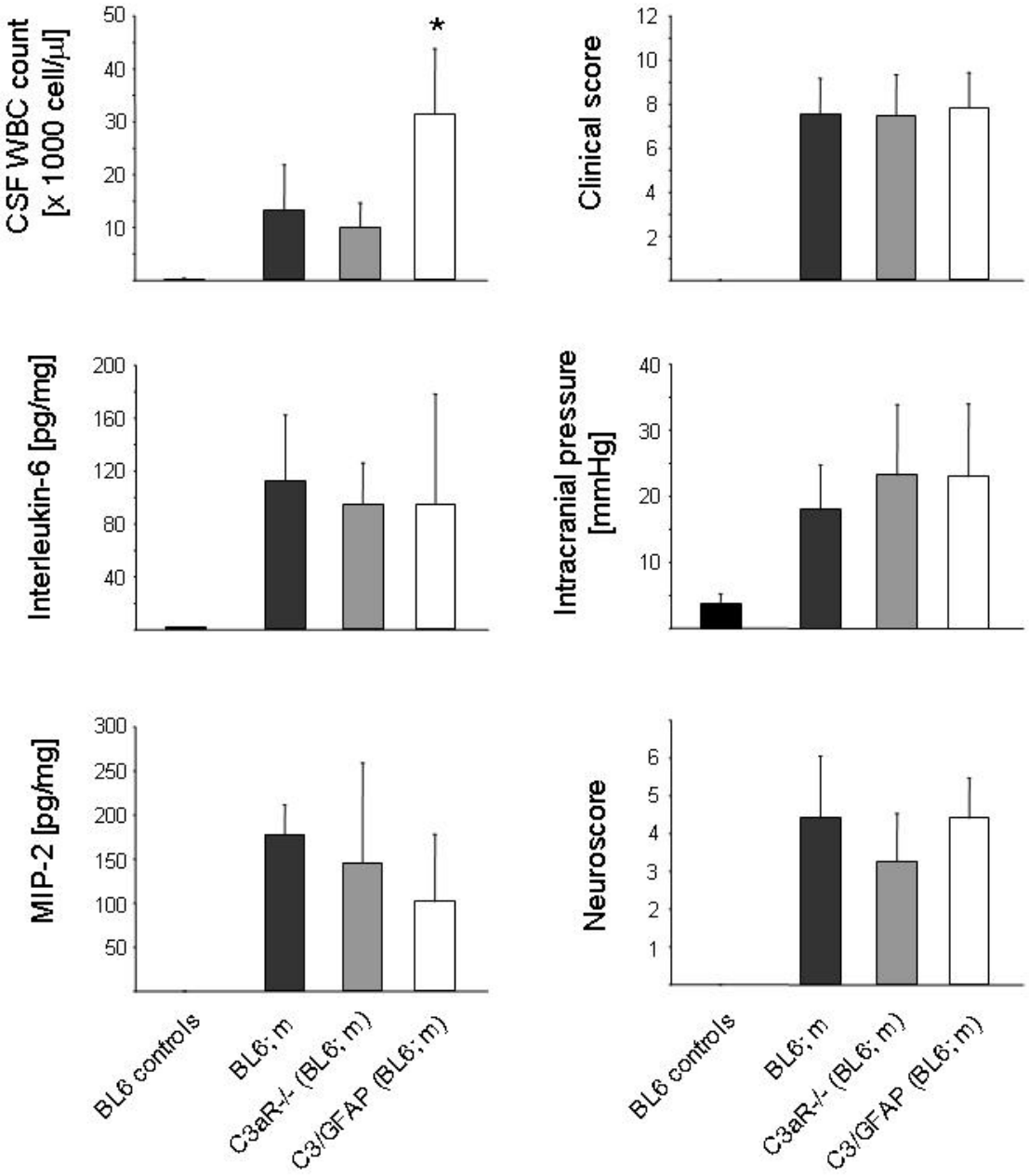
Supplementary Figure 2: Role of the membrane attack complex (MAC) in the mouse model of pneumococcal meningitis.



To evaluate the role of MAC, mice deficient in C6 (*C6-/-*, n = 14) and thus unable to form MAC and mice deficient in CD59 (*Cd59a-/-*, n = 11), the in vivo inhibitor of MAC, were examined. Animals were infected with *S. pneumoniae* and evaluated at 24 h after infection for CSF leukocyte count (CSF WBC count), clinical score, intracranial pressure (ICP), blood brain barrier-breaching and intracerebral hemorrhage combined in the neuroscore and expression of proinflammatory mediators and cytokines, namely Interleukin-6 and MIP-2. Infected mouse

mutants were compared to infected wt mice (C57BL/6 (BL6), f = female, n = 20). C57BL/6 mice intracisternally injected with PBS served as controls (BL6 controls, n = 8). Compared to infected wt mice and infected *C6*-/- mice, *Cd59a*-/- had significantly increased CSF WBC count. There was no difference in any of the other evaluated parameters (unpaired Student's test; data are shown as means ± SD).

Supplementary Figure 3: Role of C3a in the mouse model of pneumococcal meningitis.



To evaluate the role of C3a, mice deficient in the C3a-receptor (*C3ar1*-/-, n = 12) and mice with selective expression of C3a in the CNS (C3a/GFAP, n = 11) were examined. Animals were infected with *S. pneumoniae* and evaluated at 24 h after infection for CSF leukocyte count (CSF WBC count), clinical score, intracranial pressure (ICP), blood brain barrier-breaching and intracerebral hemorrhage combined in the neuroscore and expression of proinflammatory

mediators and cytokines, namely Interleukin-6 and MIP-2. Infected mouse mutants were compared to infected wt mice (C57BL/6 (BL6), m = male, n = 12). C57BL/6 mice intracisternally injected with PBS served as controls (BL6 controls, n = 8). Compared to infected wt mice and infected *C3ar1*-/- mice, C3/GFAP mice had significantly increased CSF WBC count. There was no difference in any of the other of the evaluated parameters (unpaired Student's test; data are shown as means ± SD).

SUPPLEMENTAL METHODS

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