Research

Prevalence of antimicrobial resistance in bacteria isolated from central nervous system specimens as reported by U.S. hospital laboratories from 2000 to 2002

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Abstract

Background: Bacterial infections of the central nervous system, especially acute infections such as bacterial meningitis require immediate, invariably empiric antibiotic therapy. The widespread emergence of resistance among bacterial species is a cause for concern. Current antibacterial susceptibility data among central nervous system (CNS) pathogens is important to define current prevalence of resistance.

Methods: Antimicrobial susceptibility of pathogens isolated from CNS specimens was analyzed using The Surveillance Database (TSN®) USA Database which gathers routine antibiotic susceptibility data from >300 US hospital laboratories. A total of 6029 organisms derived from CNS specimen sources during 2000–2002, were isolated and susceptibility tested.

Results: *Staphylococcus aureus* (23.7%) and *Streptococcus pneumoniae* (11.0%) were the most common gram-positive pathogens. Gram-negative species comprised approximately 25% of isolates. The modal patient age was 1 or <1 year for most organisms. Prevalence of MRSA among *S. aureus* from cerebrospinal fluid (CSF) and brain abscesses were 29.9–32.9%. Penicillin resistance rates were 16.6% for *S. pneumoniae*, 5.3% for viridans group streptococci, and 0% for *S. agalactiae*. For CSF isolates, ceftriaxone resistance was *S. pneumoniae* (3.5%), *E. coli* (0.6%), *Klebsiella pneumoniae* (2.8%), *Serratia marcescens* (5.6%), *Enterobacter cloacae* (25.0%), *Haemophilus influenzae* (0%). *Listeria monocytogenes* and *N. meningitidis* are not routinely susceptibility tested.

Conclusions: Resistance is commonly detected, albeit still at relatively low levels for key drugs classes such as third-generation cephalosporins. This data demonstrates the need to consider predominant resistance phenotypes when choosing empiric therapies to treat CNS infections.

Background

Infections of the central nervous system (CNS) are potentially life threatening, requiring rapid diagnosis and immediate parenteral treatment. Nearly one in four adults with acute bacterial meningitis will die and many survivors sustain neurological deficits. Patient outcomes have not changed since the early 1960s, despite the introduction of potent antibiotics and specialized intensive care units [1]. Many infectious agents reach the CNS by hematogenous spread [2]. Pneumococcal infection may also arise from chronic infection of the paranasal sinuses and or middle ear. Furthermore, organisms present in the nasopharynx may reach the CNS directly, if the dura mater is damaged in some way following head injury or surgery [2]. Bacterial pathogens isolated from the CNS in patients with symptoms and diagnostic signs of bacterial meningitis are *Streptococcus pneumoniae*, *Streptococcus agalactiae* and other gram-positive cocci, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Escherichia coli* [3,4]. The epidemiology of infectious agent varies with patient age and history of immunization against *Haemophilus influenzae* type b, meningococcus and pneumococcus. *N. meningitidis* is now the most common cause of meningitis in young people with a peak incidence at 6 months age coinciding with the loss of maternal antibody protection [5], whilst pneumococcal meningitis is the most common bacterial meningitis in middle-aged and elderly patients [3,4].

The need to treat infections of the CNS immediately requires empiric choice of an antibacterial agent. For many years β-lactams have comprised the cornerstone of therapy and parenteral third-generation cephalosporins such as ceftriaxone or cefotaxime are most commonly used [6]. Where infection is likely to have occurred from another body site, available laboratory information on identification and antibiogram of the organism can help target therapy appropriately. The emergence of antibiotic resistance in *S. pneumoniae*, *Staphylococcus aureus*, and enteric gram-negative bacilli documents the need for susceptibility testing to ensure appropriate antimicrobial chemotherapy. In contrast to community respiratory infections, for which antimicrobial susceptibility surveillance studies are frequently published, few data are available to provide a current perspective on the relative incidence and antibiotic susceptibility profiles bacterial pathogens isolated from CNS clinical specimens. In the routine clinical laboratory the majority of bacterial pathogens identified and tested are derived from the cerebrospinal fluid (CSF), most likely from patients with meningitis, and less commonly from brain abscesses, epidural abscesses or shunt/devices.

This study was undertaken to provide a current picture of bacterial pathogens commonly isolated from CSF and other CNS specimens by hospital laboratories participating in The Surveillance Network (TSN) Database USA during 2000–2002.

Methods

TSN hospital laboratory and antimicrobial susceptibility testing methodology

TSN Database comprises a network of hospital laboratories throughout the USA. The number of participant hospitals that susceptibility test bacterial isolates from CNS specimens was 154 (2000), 155 (2001), and 153 (2002). Susceptibility data are collected onsite by each participating laboratory as a part of their routine diagnostic susceptibility testing. Methods used by these laboratories include predominantly VITEK (bioMérieux, St. Louis, MO) and MicroScan (Dade-Microscan, Sacramento, CA). TSN reflects current testing in participant laboratories and is the data reported to physicians from the respective laboratories. Only susceptibility data interpreted according to the recommendations established by the National Committee for Clinical Laboratory Standards (NCCLS) [7] are included in TSN. Bacterial isolates not tested for susceptibility to antimicrobial agents are not included in this database. In addition, TSN uses a series of quality-control filters (i.e., critical rule sets) to screen susceptibility test results for patterns indicative of testing error and removes suspect results from analysis for laboratory confirmation.

Bacterial species and antimicrobials tested

We included only data on bacteria isolated from CNS clinical specimens, which comprised mostly isolates from CSF (most likely from patients with meningitis), but also isolates from brain abscesses, epidural abscess and shunt/devices. All specimens were isolated from patients during January 1, 2000 through December 31, 2002. Data were analyzed to determine the relative incidence and susceptibility to a core set of antimicrobial agents relevant to the treatment of CNS infections, as tested by participant clinical laboratories. For each organism only antibiotics for which susceptibility data were available were listed. Thus, drugs listed vary per organism. No susceptibility data for colistin for gram-negative organisms were available through TSN. MICs were interpreted as susceptible, intermediate, or resistant in TSN according to 2003 breakpoint criteria defined by the NCCLS [8]. TSN was not able to distinguish between community-acquired or hospital-acquired infection. In addition, TSN was not able to determine whether some isolates for which susceptibility data were requested, were actually contaminants and not true pathogens. Data available through TSN did not allow the identification of *H. influenzae* as encapsulated or as type b strains. No NCCLS interpretive breakpoints were defined for *N. meningitides*, so few laboratories susceptibility test this organism.

Table 1: Relative incidence of bacterial species isolated from central nervous system specimens. TSN Database USA 2000–2002.

Organism	Number of organisms	Percentage of total	Patient age range (year)	Modal Patient age (year)
Staphylococcus aureus	1426	23.7	<1 – >90	<1
Streptococcus pneumoniae	661	11.0	<1 – >90	1
Viridans group streptococci	612	10.2	<1 – 88	<1
Enterococcus spp.	590	9.8	<1 – >90	<1
Escherichia coli	302	5.0	<1 – 89	<1
Pseudomonas aeruginosa	295	4.9	<1 – >90	<1
Enterobacter cloacae	260	4.3	<1 – 84	<1
Coagulase-negative staphylococci [a]	184	3.1	<1–>90	1
Acinetobacter baumannii	162	2.7	<1 – 84	<1
Klebsiella pneumoniae	151	2.5	<1 – 83	<1
Streptococcus agalactiae	131	2.2	<1 – 83	<1
Serratia marcescens	127	2.1	<1 – 85	<1
Proprionibacterium acnes	118	2.0	<1 – 82	33
Enterobacter aerogenes	103	1.7	<1 – 84	<1
Haemophilus influenzae	75	1.2	<1 – >90	<1
Klebsiella oxytoca	62	1.0	<1 – 69	<1
Neisseria meningitidis	60	1.0	<1 – 70	2
Corynebacterium spp.	58	1.0	<1 – 87	16
Other [b]	652	10.8	<1 – >90	<1
Total	6029	100		

[a]Coagulase-negative staphylococci only includes isolates associated with shunt/device infections [b]Organisms isolated at a frequency of <0.5%.

Results

During the 3-year time period considered, a total of 6029 organisms were isolated and susceptibility tested (Table 1). More than 90% of all organisms were derived from CSF, the remainder from brain or epidural abscess or shunt/device infections. The most common gram-positive isolates were *S. aureus* (23.7%), *S. pneumoniae* (11.0%), viridans group streptococci (VGS) (10.2%), and *Enterococcus* species (9.8%). *S. agalactiae* (2.2%), coagulase-negative staphylococci (shunt/device infections only) (3.1%), *Propionibacterium acnes* (2.0%) and *N. meningitidis* (1.0%) were comparatively rare. *E. coli* (5.0%), *Enterobacter cloacae* (4.3%), *Klebsiella pneumoniae* (2.5%) and *S. marcescens* (2.1%) were the most common *Enterobacteriaceae*. *Pseudomonas aeruginosa* (4.9%) was equally as common as *E. coli*. Although *N. meningitidis* comprised just 60/6029 isolates during the 3-year period the organism was likely under-represented because organisms included in this study were only those accompanied by a susceptibility test result. The modal age of patients was 1 or <1 year for all organisms except for *P. acnes* (33 years), *N. meningitidis* (2 years) and *Corynebacterium* spp. (16 years). *H. influenzae* was rare. For enteric bacilli, staphylococcal, *P. aeruginosa* and *Acinetobacter* spp. a second smaller incidence peak, primarily with isolates derived from shunt infections and from CSF, was detected for patients >65 years (data not shown).

Susceptibility of coagulase-positive or -negative staphylococcal species (shunt isolates only) was shown (Table 2). *S. aureus* was the most common pathogen tested at all sites of infection. The proportion of *S. aureus* testing as MRSA using oxacillin as marker was 29.9%, 32.9%, 15.5% and 16.7% from CSF, brain abscess, shunt/device related or epidural abscess specimen sources, respectively. For coagulase-negative staphylococci 67.2% of isolates were oxacillin-resistant. Overall for all organisms, shunt isolates comprised <2.0 % of all isolates isolated and tested from CNS sources during this time period, comprising mainly staphylococcal species. Parenteral cephalosporins were not active against MRSA but generally active against >99% of oxacillin-susceptible isolates based on NCCLS breakpoints for non-CNS infections. All staphylococci were vancomycin susceptible. Low levels of resistance to gentamicin, chloramphenicol, trimethoprim-sulfamethoxazole and rifampin were detected, although resistance tended to be higher among coagulase-negative staphylococci.

Table 3 shows susceptibility for the other most common gram-positive organisms derived from CSF. VGS were isolated in significant numbers only from brain abscesses. For isolates from CSF specimens, resistance among enterococci varied by species. The prevalence of vancomycin resistance among *E. faecium* was 61.5% and the prevalence of resistance to ampicillin, the class representative

Table 2: Susceptibility of staphylococcal species isolated from cerebrospinal fluid, brain abscess, shunt related and epidural specimen sources. TSN Database USA 2000–2002.

Organism	Antimicrobial	Cerebrospinal fluid			Brain abscess			Shunt related			Epidural abscess		
		Total n	%S[a]	%R	Total n	%S	%R	Total n	%S	%R	Total n	%S	%R
Staphylococcus aureus	cefotaxime	270	74.8	25.2	12	75.0	25.0	10	90.0	10.0	NA[b]	NA	NA
	ceftriaxone	273	71.8	27.8	13	76.9	23.1	18	88.9	11.1	NA	NA	NA
	levofloxacin	666	73.1	22.8	48	72.9	27.1	33	97.0	3.0	83	79.5	18.1
	chloramphenicol	277	95.3	1.4	6	100	0	9	88.9	0	NA	NA	NA
	gentamicin	941	93.0	6.8	65	93.8	4.6	53	94.3	5.7	38	97.4	2.6
	oxacillin	1189	70.1	29.9	76	67.1	32.9	71	84.5	15.5	108	83.3	16.7
	rifampin	851	96.9	2.5	51	100	0	48	91.7	6.3	24	100	0
	TMP-SMX[c]	1058	95.9	4.1	72	94.4	5.6	47	100	0	101	96.0	4.0
	vancomycin	1150	100	0	76	100	0	58	100	0	102	100	0
Coagulase-negative staphylococci (shunt-related only)	cefotaxime	ND[d]	ND	ND	ND	ND	ND	32	34.4	65.6	ND	ND	ND
	ceftriaxone	ND	ND	ND	ND	ND	ND	37	35.1	64.9	ND	ND	ND
	levofloxacin	ND	ND	ND	ND	ND	ND	75	82.7	5.3	ND	ND	ND
	chloramphenicol	ND	ND	ND	ND	ND	ND	22	95.5	0	ND	ND	ND
	gentamicin	ND	ND	ND	ND	ND	ND	124	75.8	22.6	ND	ND	ND
	oxacillin	ND	ND	ND	ND	ND	ND	183	32.8	67.2	ND	ND	ND
	rifampin	ND	ND	ND	ND	ND	ND	108	92.6	6.5	ND	ND	ND
	TMP-SMX	ND	ND	ND	ND	ND	ND	114	77.2	22.8	ND	ND	ND
	vancomycin	ND	ND	ND	ND	ND	ND	161	100	0	ND	ND	ND

[a]NCCLS interpretation for susceptible (S) and resistant (R) according to NCCLS guidelines [8] [b]NA – <5 organisms tested [c]TMP-SMX – Trimethoprim-sulfamethoxazole [d]ND – No data

for amino-penicillins, was 84.9%. Significantly less resistance was detected among *E. faecalis* isolates. Ceftriaxone resistance rates were recorded in 9.1% of VGS, 3.5% of *S. pneumoniae*, and 0% of *S. agalactiae* (data not tabulated), although more active than cefotaxime. Penicillin resistance was recorded in 5.3% of VGS, 16.6% of *S. pneumoniae*, and 0% of *S. agalactiae* (data not tabulated). For *S. pneumoniae* meropenem resistance was recorded in 7.9% of isolates but was not detected in other streptococcal species. Resistance to chloramphenicol among streptococci was uncommon (3–3.9%). Rifampin resistance ranged from 17.2% to 30.0% among enterococci and was not recorded among *S. pneumoniae*. TMP-SMX resistance was common among *S. pneumoniae*. Resistance in VGS from brain abscesses to ceftriaxone and penicillin was recorded as 3.0% and 1.4%, respectively, with organisms generally more susceptible than those isolated from CSF specimens. With the exception of a small number of VGS from CSF specimens, all streptococci were susceptible to levofloxacin.

Susceptibility of predominant gram-negative species isolated from CSF specimens was shown (Table 4). Gram-negative isolates were rarely isolated from brain abscess, shunt, or epidural abscess specimens. No meropenem resistance was detected in *Enterobacteriaceae* but detected in 10.3% and 23.5% of *P. aeruginosa* and *A. baumanii*.

Resistance to amikacin was rare among *Enterobacteriaceae* and was 4.9% for *P. aeruginosa* and 17.9% for *Acinetobacter* spp. Among enteric organisms the prevalence of resistance was low against ceftriaxone for *E. coli* (0.6%), *E. aerogenes* (1.6%), and *K. pneumoniae* (2.8%) and were higher for *S. marcescens* (5.6%), *K. oxytoca* (13.3%), and *E. cloacae* (25.0%). Resistance to ceftazidime was 1.4% and 18.0 % in *E. coli* and *K. pneumoniae*, respectively. For *Enterobacteriaceae*, aztreonam resistance ranged from 1.5% in *E. coli* to 26.5% in *E. cloacae*. Levofloxacin resistance rates were uncommon in all *Enterobacteriaceae* tested apart from *K. pneumoniae* (9.2%). For *P. aeruginosa* the prevalence of ceftazidime and amikacin resistance was 11.0% and 4.9%, respectively and for *A. baumanii* 38.7% and 17.9%, respectively. For both of these organisms relatively high resistance to levofloxacin was detected and meropenem was the most active β-lactam compound tested with resistance recorded as 10.3% and 23.5%, respectively. Approximately 24.0% of *H. influenzae* produced β-lactamase as estimated by ampicillin resistance. All *H. influenzae* isolates tested were susceptible to cefotaxime, ceftriaxone, and levofloxacin.

Discussion
Vaccination against infections with *H. influenzae* and *N. meningitidis* has significantly reduced the incidence of community-acquired infections caused by these organ-

Table 3: Susceptibility of gram-positive organisms isolated from cerebrospinal fluid and brain abscess specimen sources. TSN Database USA 2000–2002.

Organism	Antimicrobial	Cerebrospinal fluid			Brain abscess		
		Total n	%S[a]	%R	Total n	%S	%R
Enterococcus faecalis	ampicillin	229	98.7	1.3	ND[b]	ND	ND
	chloramphenicol	79	79.7	15.2	ND	ND	ND
	levofloxacin	136	81.6	18.4	ND	ND	ND
	penicillin	165	99.4	0.6	ND	ND	ND
	rifampin	58	58.6	17.2	ND	ND	ND
	vancomycin	239	98.7	1.3	ND	ND	ND
Enterococcus faecium	ampicillin	93	15.1	84.9	ND	ND	ND
	chloramphenicol	54	92.6	0	ND	ND	ND
	levofloxacin	56	12.5	85.7	ND	ND	ND
	penicillin	50	22.0	78.0	ND	ND	ND
	rifampin	30	56.7	30.0	ND	ND	ND
	vancomycin	96	38.5	61.5	ND	ND	ND
Viridans group Streptococci	ampicillin	95	62.1	6.3	10	90.0	0
	cefotaxime	174	85.1	9.8	32	96.9	3.1
	ceftriaxone	220	87.3	9.1	33	93.9	3.0
	chloramphenicol	100	96.0	3.0	14	92.9	0
	meropenem	19	100	0	13	100	0
	levofloxacin	90	96.7	1.1	24	100	0
	penicillin	437	63.2	5.3	72	97.2	1.4
	vancomycin	396	100	-[e]	44	100	0
Streptococcus pneumoniae	cefotaxime	313	80.5	7.7 (19.5 NS[c])	ND	ND	ND
	ceftriaxone	404	85.4	3.5 (14.6 NS)	ND	ND	ND
	chloramphenicol	180	96.1	3.9 (3.9 NS)	ND	ND	ND
	meropenem	76	78.9	7.9 (21.1 NS)	ND	ND	ND
	levofloxacin	283	100	0	ND	ND	ND
	penicillin	565	59.5	16.6 (40.5 NS)	ND	ND	ND
	rifampin	70	100	0	ND	ND	ND
	TMP-SMX[d]	233	65.2	27.5 (34.8 NS)	ND	ND	ND
	vancomycin	453	100	-	ND	ND	ND

[a]NCCLS interpretation for susceptible (S) and resistant (R) according to NCCLS guidelines [8] [b]ND – No data [c]NS – Percent non-susceptible (including intermediate and resistant isolates) [d]TMP-SMX – Trimethoprim-sulfamethoxazole [e]Dashed line indicates that NCCLS breakpoints do not currently exist to interpret results as resistant

isms [9,10]. Additionally, the growing use of the pneuo-coccocal conjugate vaccine has also had a positive impact on the incidence of pneumococcal meningitis [11,12]. Since clinicians will likely initiate antimicrobial therapy prior to the microbiological characterization of the infecting agent, with the reduction in incidence of some species and increased resistance in others, resistance surveillance plays an important role in helping to understand trends in predominant pathogens and the impact of resistance on empiric choice [13]. The TSN database was not able to discriminate between specific diagnoses; however, considering bacterial pathogens isolated from specific specimen sources provides a contemporary picture of current susceptibility to commonly considered antimicrobial agents for the most prevalent organisms encountered at these sites of infections.

For the most significant community-acquired pathogens, this study showed similarities between epidemiological trends recently published. For meningitis in the USA, a report by Schuchat et al., 1997, recorded a significant shift from 15 months to 25 years, in the median age of patients with meningitis due to the five major pathogens: *H. influenzae*, *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, and *L. monocytogenes* [3]. Overall including all specimen sources together, although the majority of isolates were derived from the CSF, our study showed that isolates were derived from a wide spectrum of patient ages. However with few exceptions, the modal age of patients was ≤1 year old, demonstrating the burden of infection to be with infants and with a second peak for patients >65 years [3].

Table 4: Susceptibility of gram-negative organisms isolated from cerebrospinal fluid specimen sources. TSN Database USA 2000–2002

Organism	Antimicrobial	Total n	%S[a]	%R
Escherichia coli	amikacin	164	98.8	0
	ampicillin	267	44.2	54.7
	aztreonam	137	96.4	1.5
	cefotaxime	168	98.2	0
	ceftazidime	210	98.1	1.4
	ceftriaxone	180	97.8	0.6
	gentamicin	260	93.5	5.4
	levofloxacin	198	97.5	2.5
	meropenem	76	100	0
	piperacillin	188	50.0	38.8
	TMP-SMX[b]	252	77.0	23.0
Pseudomonas aeruginosa	amikacin	184	92.9	4.9
	aztreonam	133	67.7	15.0
	cefotaxime	111	9.0	49.5
	ceftazidime	236	80.1	11.0
	ceftriaxone	116	6.0	61.2
	gentamicin	251	80.9	11.2
	levofloxacin	174	82.2	11.5
	meropenem	97	84.5	10.3
	piperacillin	198	82.8	17.2
	TMP-SMX	128	0.8	99.2
Enterobacter cloacae	amikacin	160	98.8	0
	ampicillin	229	2.2	91.7
	aztreonam	147	65.3	26.5
	cefotaxime	154	63.6	28.6
	ceftazidime	196	67.3	29.6
	ceftriaxone	184	70.7	25.0
	gentamicin	227	95.2	4.8
	levofloxacin	176	96.0	4.0
	meropenem	79	100	0
	piperacillin	168	64.9	28.0
	TMP-SMX	220	93.2	6.8
Acinetobacter baumannii	amikacin	112	75.0	17.9
	aztreonam	88	8.0	73.9
	cefotaxime	102	21.6	54.9
	ceftazidime	142	48.6	38.7
	ceftriaxone	119	25.2	53.8
	gentamicin	143	61.5	38.5
	levofloxacin	106	53.8	43.4
	meropenem	68	75.0	23.5
	piperacillin	111	40.5	40.5
	TMP-SMX	140	54.3	45.7
Klebsiella pneumoniae	amikacin	95	92.6	0
	ampicillin	129	0	98.4
	aztreonam	70	84.3	14.3
	cefotaxime	94	87.2	3.2
	ceftazidime	111	76.6	18.0
	ceftriaxone	108	84.3	2.8
	gentamicin	131	87.8	8.4
	levofloxacin	98	88.8	9.2
	meropenem	47	100	0
	piperacillin	102	65.7	26.5
	TMP-SMX	133	83.5	16.5
Serratia marcescens	amikacin	71	95.8	2.8
	ampicillin	104	5.8	92.3
	aztreonam	55	87.3	7.3
	cefotaxime	70	80.0	8.6
	ceftazidime	86	93.0	4.7
	ceftriaxone	71	91.5	5.6

Table 4: Susceptibility of gram-negative organisms isolated from cerebrospinal fluid specimen sources. TSN Database USA 2000–2002

	gentamicin	108	95.4	2.8
	levofloxacin	80	98.8	1.3
	meropenem	43	100	0
	piperacillin	81	72.8	21.0
	TMP-SMX	105	95.2	4.8
Enterobacter aerogenes	amikacin	60	100	0
	ampicillin	87	5.7	87.4
	aztreonam	42	73.8	11.9
	cefotaxime	54	74.1	1.9
	ceftazidime	78	73.1	17.9
	ceftriaxone	63	84.1	1.6
	gentamicin	81	100	0
	levofloxacin	51	100	0
	meropenem	22	100	0
	piperacillin	64	68.8	14.1
	TMP-SMX	85	100	0
Haemophilus influenzae	ampicillin	61	72.1	24.6
	cefotaxime	27	100	-d
	ceftazidime	NAc	NA	NA
	ceftriaxone	54	100	-
	levofloxacin	10	100	-
	TMP-SMX	32	87.5	9.4
Klebsiella oxytoca	amikacin	37	100	0
	ampicillin	52	3.8	86.5
	aztreonam	34	76.5	17.6
	cefotaxime	37	81.1	16.2
	ceftazidime	44	81.8	18.2
	ceftriaxone	45	84.4	13.3
	gentamicin	51	96.1	3.9
	levofloxacin	39	100	0
	meropenem	23	100	0
	piperacillin	38	73.7	21.1
	TMP-SMX	51	80.4	19.6

aNCCLS interpretation for susceptible (S) and resistant (R) according to NCCLS guidelines [8] bTMP-SMX – Trimethoprim-sulfamethoxazole cNA <5 organisms tested dDashed line indicates that NCCLS breakpoints do not currently exist to interpret results as resistant

The low comparative prevalence of *H. influenzae* indicates the success of the Hib vaccination program, which has largely removed this organism from its once ubiquitous role in meningeal infection in children in the United States [14]. Schuchat et al. also reported *L. monocytogenes* to be associated with infections in children <1 year old and increases in incidence in patients older than 65 years. In this current study, the relative importance of both *L. monocytogenes* and *N. meningitidis* in infection cannot be measured since the organisms were rarely tested for antimicrobial susceptibilities in hospital laboratories and thus not reported through the system. Additionally, no NCCLS breakpoints have been defined for *N. meningitidis* [9]. Invasive pneumococcal disease is a significant cause of morbidity and mortality in the USA, especially for the young and old. Schuchat et al. demonstrated *S. pneumoniae* to infect patients of all ages, the same trend observed in our study. We also showed that with the exception of staphylococci, *S. pneumoniae* was the most common pathogen reported. A previous report showed 4.4% of cases of

invasive pneumococcal disease associated with meningitis [3]. Further analysis of TSN showed that during the study period laboratories reported 661 non-repeat CNS pneumococcal isolates and 9868 non-repeat pneumococcal blood isolates, corresponding to a 6–7% rate of patients with invasive infections likely to be associated with pneumococcal meningitis, close to the 4–5% reported in 1995 [3]. This study also showed *Enterobacteriaceae* to be more common in hospital-acquired meningeal infections. *S. aureus* was by far the most frequently encountered pathogen in participant hospital laboratories, in this study together comprising 23.7% of isolates and the only isolate encountered at all specimen source sites considered. A previous French study showed *S. aureus* to be the most common pathogen associated with neurosurgical infections [15]. In addition to the staphylococci, *Enterococcus* spp., *P. aeruginosa*, *P. acnes*, and *Enterobacteriaceae* were most commonly isolated from infants (<1 year old), although the median age also demonstrates the common involvement in adult patients. Together these organisms

are becoming common causes of meningeal infection, often as a complication in immunocompromised patients, in patients with septicemia, following head trauma, or surgical procedures especially those involving CSF shunts.

The relatively high incidence of oxacillin-resistant *S. aureus* from CSF and brain abscesses negatively impacts the empiric utility of isoxazolyl penicillins reaffirming the need to include anti-MRSA coverage for patients with meningitis and brain abscesses, unless subsequent susceptibility testing shows the organism to be oxacillin susceptible. Even among isolates from shunts and epidural abscesses the 15–17% incidence of oxacillin resistance likely mandates the use of empiric therapies such as vancomycin that cover MRSA. However, it is important to note that these levels are lower than the national rates of MRSA of 51.2% (36,181/70,693) recorded among the general inpatient population in the USA during 2002 [TSN Database USA, Focus Technologies Inc. Data on file]. Susceptibility test results for MRSA to linezolid, a recently FDA-approved oxazolidinone-class antibiotic, and daptomycin, a recently approved glycopeptide-class antibiotic, were not available at the time of this study, although neither drugs have indications to treat infections of the central nervous system. Interestingly, despite an overall increase in the incidence of MRSA in hospitals in recent years in both inpatient and outpatient environments [16] an increased incidence of multi-drug suscepti-ble MRSA, especially in community infections, has also been reported [17], which may augment the use of other compounds such as clindamycin in therapy. For shunt/ device related infections, the high rates of oxacillin resistance recorded among coagulase-negative staphylococci indicate the need to consider appropriate therapies to cover these phenotypes. For both staphylococcal species resistance to rifampin, occasionally used in combination, was rare, comprising 0–6.5% of isolates from each species, respectively. Despite reports of vancomycin resistance in coagulase-negative staphylococci [18] and more recently *S. aureus* [19,20], during the three-year study period, no vancomycin non-susceptible isolates of either species were recorded. Vancomycin also plays an important role in the treatment of other resistant gram-positive infections, most importantly those caused by penicillin-resistant *S. pneumoniae* (penicillin MIC >2 µg/ml), for which no resistance was documented. Of the 661 isolates reported during the study period (11.0% of total), 16.6% and 23.9% tested as penicillin-resistant and -intermediate, respectively. For meningitis caused by pneumococci and in situations where the incidence of penicillin resistance is significant, the use of third-generation, parenteral cephalosporins such as ceftriaxone or cefotaxime is a more suitable empiric therapy. The percentage resistance to third-generation cephalosporins for the common strep-

tococcal isolates from CSF, likely involved in meningeal infection, remained low (3.5% for ceftriaxone); however, concerns about resistance in CNS infections are sufficient to prompt recommendations to combine ceftriaxone or cefotaxime with vancomycin for empiric therapy of pneumococcal CNS infections. The reported rate of resistance in *S. pneumoniae* to ceftriaxone and cefotaxime reflects the higher breakpoints used compared to those used for non-meningeal pneumococcal isolates, reflecting the lower antibiotic concentrations achievable in the CNS. Importantly in addition to streptococci, 100% of *H. influenzae* tested as susceptible to ceftriaxone and cefotaxime. As such the utility of this drug class in community or hospital acquired infections meningeal infections with these organisms remains unchanged.

The incidence of vancomycin-resistant phenotypes among enterococci, organisms not commonly associated with meningeal infections, is alarming if the organisms isolated were colonizers. Importantly, the majority of glycopeptide-resistant isolates are *E. faecium*, which are less common than *E. faecalis*.

Our study showed resistance to amikacin remained very low (0–2.8%) among *Enterobacteriaceae* and low among *Acinetobacter* spp. and *P. aeruginosa* (17.9% and 4.9%, respectively), although the utility of this agent is limited in CNS infections. Importantly, bearing in mind their role in empiric therapy for meningitis, resistance to third-generation cephalosporins such as ceftriaxone, remained very uncommon in the common enterobacterial species (*E. coli* 0.6%, *K. pneumoniae* 2.6%, and *S. marcescens* 5.2%). Resistance to ceftazidime in these species was somewhat higher than for ceftriaxone. Together these data suggest that the incidence of extended spectrum β-lactamases or AmpC β-lactamase producers still remains low, preventing a reliance on the use of carbapenems such as meropenem to which resistance among gram-negative organisms remains very rare. Changing patterns of antimicrobial resistance and the involvement of unusual species because of the increase in immunocompromised patients, has created renewed interest in drugs such as fluoroquinolones, which have previously been shown to have good potential for treating meningitis [21], although currently do not have an indication for use in CNS infection or in pediatrics. Nevertheless using levofloxacin as a marker for this drug class activity, streptococci, several species of *Enterobacteriaceae* and *H. influenzae* were highly susceptible using current breakpoint guidelines.

Conclusions
Several factors influence the choice of antibacterial agent in the treatment of bacterial meningitis. Perhaps most importantly is the degree at which the agent is able to penetrate into the CSF, which to a large extent depends on the

status of the blood brain barrier [22]. Low toxicity and rapid bactericidal activity are also important factors to consider and for these reasons β-lactams have always played a key role in treating infections of the CNS. Our study showed that for the treatment of the most important pathogens associated with acute community-acquired meningitis including *S. pneumoniae*, *H. influenzae*, and group B streptococci, while resistance to penicillin derivatives is relatively common, resistance to third-generation cephalosporins remains uncommon. Similarly, third-generation cephalosporins also retain good activity against the most common species of *Enterobactericeae*. For infections in which oxacillin-resistant staphylococcal species are suspected or shown microbiologically, vancomycin remains as a frontline agent to which no resistant isolates were detected through 2002. While national surveillance studies such as this are able to detect general trends in susceptibility, this information combined with local institutional level data play a critical role in choosing empiric therapies.

Authors' contributions

MJ conceived the study, provided data interpretation and drafted the manuscript. DD analyzed the study data; JK and DS provided expert microbiological analysis and interpretation of study data; JB provided clinical expertise in interpretation of data and drafting manuscript. All authors read and approved the final manuscript.

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