ORIGINAL ARTICLE INFECTIOUS DISEASES

Intrathecal colistin for drug-resistant *Acinetobacter baumannii* central nervous system infection: a case series and systematic review

T. Khawcharoenporn[1], A. Apisarnthanarak[1] and L. M. Mundy[2]

1) Division of Infectious Diseases and Infection Control, Faculty of Medicine, Thammasart University Hospital, Pratumthani, Thailand and 2) LM Mundy, LLC, Bryn Mawr, PA, USA

Abstract

Treatment limitations exist for drug-resistant *Acinetobacter baumannii* central nervous system (CNS) infection. We conducted a retrospective study and systematic literature review to identify patients with drug-resistant *A. baumannii* CNS infection who received primary or adjunct intrathecal or intraventricular (IT/IVT) colistin. In a case series of seven Thai patients and 17 patients identified in the literature, clinical and microbiological cure rates with IT/IVT colistin therapy were 83% and 92%, respectively. Three patients (13%) developed chemical ventriculitis and one (4%) experienced treatment-associated seizures. Death was associated with delayed IT/IVT colistin therapy compared to survival (mean time from diagnosis to IT/IVT colistin, 7 vs. 2 days; p 0.01). The only independent predictor of mortality was the severity of illness (APACHE II score > 19, adjusted odds ratio 49.5; 95% CI 1.7–1428.6; p 0.02). This case series suggests that administration of primary or adjunctive IT/IVT colistin therapy was effective for drug-resistant *A. baumannii* CNS infection.

Keywords: *Acinetobacter baumannii*, central nervous system, colistin, intrathecal, intraventricular, meningitis, multidrug-resistant, pandrug-resistant
Original Submission: 2 March 2009; **Revised Submission:** 18 June 2009; **Accepted:** 3 August 2009
Editor: M. Drancourt
Article published online: 20 October 2009
Clin Microbiol Infect 2010; **16:** 888–894
10.1111/j.1469-0691.2009.03019.x

Corresponding author and reprint requests: A. Apisarnthanarak, Division of Infectious Diseases, Faculty of Medicine, Thammasart University Hospital, Pratumthani, Thailand 12120
E-mail: anapisarn@yahoo.com

Introduction

Acinetobacter baumannii has emerged as an important multidrug-resistant (MDR) and pandrug-resistant (PDR) healthcare-associated pathogen [1–4]. Outbreaks caused by MDR *A. baumannii* have been reported from various countries, with anecdotal treatment success using aminoglycosides, carbapenems, β-lactamase inhibitors, tigecycline, rifampin and colistin [1–4]. Although intravenous (IV) carbapenems and β-lactamase inhibitors reach acceptable drug levels in the central nervous system (CNS) [5], higher than regular dose carbapenems in combination with β-lactamase inhibitors, aminoglycosides or rifampin may not be effective for PDR *A. baumannii* CNS infection [3,4].

Patients with CNS infection as a result of PDR *A. baumannii* isolates susceptible to colistin may benefit from adjunct intrathecal or intraventricular (IT/IVT) colistin therapy [2–4]. The premise for such a regimen is that IV colistin may not achieve adequate CNS penetration, IV treatment failures have been reported, and adverse events related to systemic treatment include nephrotoxicity and neurotoxicity [2,5,6]. Tigecycline is a potential alternative, yet it is not approved for meningitis treatment, and CNS pharmacokinetics and pharmacodynamics require further investigation [7,8]. The use of IT/IVT colistin and aminoglycosides has been reported for MDR/PDR *A. baumannii* meningitis with success rates of greater than 80% [9–19]. We retrospectively identified seven cases of PDR *A. baumanni* CNS infection treated with IT/IVT colistin at a Thai hospital and conducted a systematic literature review and analysis to characterize the epidemiology, risk factors, clinical manifestations, and outcomes of MDR and PDR *A. baumannii* CNS infection treated with IT/IVT colistin.

Materials and Methods

Case series: patients, study definitions and data collection

A case patient was defined as a patient who received IT/IVT colistin therapy between 1 January 2004 and 31 October 2008

at Thammasat University Hospital, a 500-bed, tertiary-care hospital in central Thailand. Case identification entailed database searches from microbiology, pharmacy and infection control. A standardized data-gathering instrument was used for retrospective medical chart review with data harvest of demographics, underlying medical conditions, neurosurgical procedures, risk factors, implanted medical devices (IMD), intensive care unit (ICU) admission, prior antibiotic use, prior *A. baumannii* colonization and length of hospitalization within 3 months of the CNS infection, clinical presentations, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, cerebrospinal fluid (CSF) profiles, culture results, colistin doses, duration of therapy, concurrent antibiotic therapy, adverse reactions (AEs) to colistin, and outcomes stratified by clinical and microbiological cure. The APACHE II scores were calculated at 24 h before the first positive CSF culture [20]. Bacterial isolation and antimicrobial susceptibility testing were performed in accordance with CLSI methodology [21]. A diagnosis of *A. baumannii* CNS infection was made on the basis of a positive CSF culture obtained from either ventricular fluid or from lumbar puncture. *Acinetobacter baumannii* was defined as MDR if resistant to all generations of cephalosporins, fluoroquinolones and aminoglycosides and PDR if resistant to all cephalosporins, fluoroquinolones, aminoglycosides, aztreonem, carbapenems and sulbactam [22]. *Acinetobacter baumannii* isolates were considered susceptible to colistin if the MIC was ≤2 mg/L and resistant if the MIC was ≥4 mg/L [21]. Inadequate antimicrobial therapy was defined as the receipt of appropriate antibiotic therapy with delay (>48 h after the positive CSF culture) or the receipt of antibiotics that were not active against the isolated microorganisms [23]. Clinical cure was defined as resolution of signs and symptoms of CNS infection, no subsequent need for additional antimicrobial therapy, and survival at hospital discharge. Microbiological cure was defined as eradication of *A. baumannnii* in subsequent cultures. The study was approved by the hospital's institutional review board.

Literature review

A comprehensive literature search was performed for reported cases of MDR or PDR *A. baumannii* CNS infection using the Pubmed database from inception through November 2008. The search was restricted to the English language, using terms 'multidrug-resistant', 'pandrug-resistant', '*A. baumannii*', 'central nervous system', 'meningitis', 'ventriculitis', 'intrathecal', 'intraventricular', 'colistin', 'colistimethate', 'treatment', 'therapy', 'case report' and 'review'. References in each manuscript were reviewed for additional and duplicate case identification of MDR or PDR *A. baumannii* CNS infection. Eleven articles were identified, with 17 cases meeting a case definition. A structured approach to the data abstraction included harvest of demographic data, clinical and laboratory characteristics, treatment and outcomes. APACHE II scores were not reported in these 17 cases. We calculated these scores for 14 of the 17 cases for whom clinical and laboratory data were reported; for the other three cases, we used the median APACHE II score.

Statistical analysis

All analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using Pearson's chi squared or Fisher's exact test as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test. All p values were two-tailed; $p < 0.05$ was considered statistically significant. The primary outcome was clinical cure. Dependent variables that were present in more than 10% of patients at a significance level of $p < 0.20$ or that had a prior clinical significance (e.g. age, APACHE-II score, receipt of inadequate antimicrobial therapy) were entered into forward stepwise logistic regression models. Significant variables that were thought to be covariates were grouped, and only one variable from each group was chosen for model entry. Adjusted ORs and 95% CIs were calculated to identify predictors of mortality.

Results

Patient characteristics and risk factors

Seven cases of PDR *A. baumanni* from the Thai hospital and 17 cases of MDR and PDR *A. baumanni* from the literature review were combined for the analysis. The participants' mean age was 38 years (range 4–74 years), at least 12 of the 24 patients were women, and all (100%) were initially admitted for neurosurgical conditions (Table 1).

Most (n = 17; 71%) participants had either head trauma or intracranial bleeding and seven (29%) had CNS tumors. Among 23 cases who had neurosurgery, 19 (83%) had craniotomy with external ventricular drain placement; four (17%) had tumor resection; two (9%) had dural grafting, and one (4%) had meningeal prosthesis placement. Eight cases (33%) with underlying medical conditions had either hypertension (n = 4; 17%), diabetes mellitus (n = 1; 4%), chronic obstructive pulmonary disease (n = 1; 4%), myocardial infarction (n = 1; 4%), solid tumor (n = 1; 4%), or prior history of *Pseudomonas aeruginosa* meningitis (n = 1; 4%).

Risk factors for *A. baumannii* included presence of a CNS IMD (n = 22; 92%), ICU admission (n = 16; 67%), prior antibiotic use (n = 16; 67%), *A. baumannii* colonization (n = 1;

8%) and prolonged hospitalization (mean 22 days; range 4–82 days). The most common antibiotic exposures were to cephalosporins (n = 10; 63% of 16 patients), followed by carbapenems (n = 7; 44%), penicillins (n = 5; 31%), vancomycin (n = 5; 31%), fluoroquinolones (n = 5; 31%), aminoglycosides (n = 4; 25%), and metronidazole (n = 1; 6%).

Clinical presentations and laboratory results (Tables 1 and 2)

Patients presented with post-operative fever (n = 16; 67%), altered mental status (n = 9; 38%), headache (n = 7; 29%), hypotension (n = 3; 13%), and seizures (n = 2; 8%). The mean APACHE II score was 16 (range 12–22), median blood leukocyte count was 16 000 cells/μL (range 15 200–32 000 cells/μL), median CSF leukocyte count was 2100 cells/μL (range 100–40 000 cells/μL); median CSF neutrophil percentage was 85% (range 68–100%); median CSF glucose level was 36 mg/dL (range 18–117 mg/dL) and median CSF protein level was 78 mg/dL (range 39–293 mg/dL). For 12 (50%) of 24 patients, Gram-negative bacilli were reported in the CSF; three (13%) had concurrent *A. baumannii* bacteraemia; 13 (54%) were infected with PDR *A. baumannii*, nine (38%) with MDR bacteria and, for two (8%), there was no report of *A. baumannii* antimicrobial susceptibility.

Treatment and outcomes (Table 2)

The median time from diagnosis to initiation of IT/IVT colistin treatment was 2 days (range 0–15 days), at a median dose of 150 000 IU/day (range 40 000–500 000 IU/day) for the median duration of 15 days (range 2–56 days). Concurrent IV antibiotics were administered to 13 (54%) of 24 cases (Table 3). Of these 13 cases, seven (54%) received

TABLE 1. Demographic characteristics, underlying diseases and clinical presentation of patients with multidrug- and pandrug-resistant *Acinetobacter baumannii* meningitis who received intrathecal/intraventricular colistin therapy

					Risk factors for antibiotic-resistant *A. baumannii*[a]					
Case No. [Reference]	Age in years/sex	Medical history[a]	CNS disease[a]	Type of surgery[a]	CNS FB	ICU admission	Prior ABX	*A. baumannii* colonization	Onset, days[b]	Presentation
1 [Present study]	72/M	HTN	Head trauma	CNT + EVD	EVD	Yes	PCN, MET	No	8	F, HA, shock
2 [Present study]	46/M	HTN, ETOH	Meningioma	CNT + EVD, T	EVD	Yes	PCN, CEP, FQ, AM	No	30	F, HA
3 [Present study]	33/Fe	None	SAH	CNT + EVD	EVD	Yes	CEP, V	No	11	F, HA, AMS
4 [Present study]	64/M	HTN, COPD, solid tumor	Medulloblastoma	CNT + EVD	EVD	Yes	PCN, CEP, FQ, CB	No	28	F, HA, AMS
5 [Present study]	22/M	None	Head trauma	CNT + EVD, EL	EVD	Yes	PCN, CEP	No	4	F, HA, AMS
6 [Present study]	41/Fe	HTN, DM	SAH	CNT + EVD	EVD	Yes	CEP	No	7	F, HA
7 [Present study]	32/Fe	None	SAH	CNT + EVD	EVD	Yes	CEP	No	15	F, HA
8 [9]	74/Fe	MI	SAH, HC	CNT + EVD	EVD	Yes	None	No	8	AMS
9 [9]	56/Fe	None	SAH, HC	CNT + EVD; CNS FB-EVD		Yes	None	No	11	ND
10 [9]	38/Fe	None	Head injury	CNT + EVD	EVD	Yes	V, CB, AM	No	40	ND
11 [9]	26/M	None	ICH	CNT + EVD	EVD	Yes	None	Yes	13	ND
12 [9]	4/M	None	Medulloblasto ma	CNT + TR	None	Yes	None	No	10	Focal seizure
13 [10]	ND	None	Head trauma	CNT + EVD	EVD	No	IV ABX	No	ND	ND
14 [10]	ND	None	Head trauma	CNT + EVD	EVD	No	IV ABX	No	ND	ND
15 [11]	16/M	None	Haemangioblas toma	CNT + TR + EV D	EVD	No	CEP, AM, CB	No	16	F
16 [11]	34/Fe	None	SAH, HC	CNT + EVD	EVD	No	None	No	7	F, AMS
17 [12]	29/M	None	SAH, skull and C-spine fractures	CNT + EVD, T	EVD	Yes	CB, FQ, V	No	28	F, AMS
18 [13]	38/Fe	Peritonitis, UTI	BC, HC	CNT + EVD	EVD	No	None	No	ND	F, Sepsis
19 [14]	61/Fe	Anorectal ulcers	Recurrent meningioma	CNT + EVD, TR, DG	EVD, DG	No	CEP, CB	No	34	F, shock
20 [15]	41/Fe	None	SAH	CNET + EVD, aneurysm clipping	EVD, clips	Yes	None	No	8	F
21 [16]	49/Fe	None	Recurrent meningioma	CNET, TR, DG	DG	Yes	PCN, CEP, CB, FQ, V	No	82	F, AMS
22 [17]	4/ND	None	Head trauma	ND	None	No	None	No	ND	ND
23 [18]	23/Fe	None	Cervical meningioma	CNT + EVD, laminectomy	EVD	Yes	CB, V, FQ	No	13	F, AMS, seizure
24 [19]	28/M	Pseudomonas meningitis	ICH	CNT, meningeal prosthesis	EVD, meningeal prosthesis	No	CEP, AM, teicoplanin	No	69	F, AMS

ABX, antibiotics; AM, aminoglycosides; AMS, altered mental status; BC, brain contusion; C, cervical; CB, carbapenems; CEP, cephalosporins; CNS, central nervous system; CNET, craniectomy; CNT, craniotomy; COPD, chronic obstructive pulmonary disease; DG, dural graft; DM, diabetes mellitus; EL, exploratory laparotomy; ETOH, alcohol abuse; EVD, external ventricular drainage; F, fever; FB, foreign bodies; Fe, female; FQ, fluoroquinolones; HA, headache; HC, hydrocephalus; HTN, hypertension; ICH, intracerebral haemorrhage; ICU, intensive care unit; IV, intravenous; M, male; MET, metronidazole; MI, myocardial infarction; ND, no data; PCN, penicillins; SAH, subarachnoid haemorrhage; T, tracheostomy; TR, tumor resection; UTI, urinary tract infection; V, vancomycin.

[a]Within the previous 3 months.

[b]Duration from the day of admission to the onset of meningitis.

TABLE 2. Diagnosis, treatment, and outcome of patients with multidrug- and pandrug-resistant *Acinetobacter baumannii* meningitis who received intrathecal/intraventricular colistin therapy

	CSF profile						IT/IVT colistin		Concurrent antibiotics				
Case No. [Reference]	WBC (cell/μL) /%*N*	Glucose (mg/dL)	Protein (mg/dL)	GS	Sites of positive culture	*A. baumannii* strain	Dose	Duration (days)	Types	Duration (days)	Time to CSF sterilization (days)[a]	Adverse reactions to IT/IVT colistin	Outcome
1 [Present study]	40 000/87	32	222	+	CSF	PDR	500 000 IU/day	2	CFP-S, CIP	1, 1	Not sterile	None	Died
2 [Present study]	8900/70	36	293	+	CSF	PDR	400 000 IU/day	4	None	-	Not sterile	None	Died
3 [Present study]	4000/100	51	78	+	CSF	PDR	400 000 IU/day	14	CFP-S	5	15	None	Cured
4 [Present study]	100/86	18	67	+	CSF	PDR	400 000 IU/day	21	Imipenem	14	10	None	Cured
5 [Present study]	2150/77	26	88	+	CSF	PDR	500 000 IU/day	15	Imipenem	22	5	None	Cured
6 [Present study]	2450/85	32	76	+	CSF	PDR	400 000 IU/day	14	None	–	3	None	Cured
7 [Present study]	2000/78	31	78	+	CSF	PDR	300 000 IU/day	18	None	–	3	None	Cured
8 [9]	ND	ND	ND	ND	CSF, EDVT	MDR	125 000 IU/day	18	Amikacin	ND	3	None	Died[b]
9 [9]	ND	ND	ND	ND	CSF	MDR	125 000 IU/day	3	Amikacin	ND	3	None	Cured
10 [9]	ND	ND	ND	ND	CSF	MDR	125 000 IU/day	12	IV colistin, amikacin	14, 14	4	CV	Cured
11 [9]	ND	ND	ND	ND	CSF, B, EVDT	MDR	125 000 IU/day	5	IV colistin, amikacin	21, 21	1	CV	Cured
12 [9]	ND	ND	ND	ND	CSF, B	MDR	50 000 IU/day	24	IV colistin, amikacin	15, 15	3	CV	Cured
13 [10]	ND	ND	ND	ND	CSF	ND	125 000 IU/day	8	None	–	Sterile	None	Cured
14 [10]	ND	ND	ND	ND	CSF	ND	250 000 IU/day	10	None	–	Sterile	None	Cured
15 [11]	27 900/95	ND	ND	ND	CSF	MDR	62 000 IU twice daily	19	IV tobramycin	21	3	None	Died[c]
16 [11]	2000/95	ND	ND	+	CSF, wound	PDR	125 000 IU twice daily	14	IV tobramycin	14	6	None	Cured
17 [12]	110/93	50	78	+	CSF	PDR	40 000 IU twice daily	28	None	–	3	None	Cured
18 [13]	355/ND	ND	270	+	CSF, PF	PDR	75 000 IU twice daily	14	None	–	Several days	Seizure	Cured
19 [14]	210/82	117	39	ND	CSF	PDR	80 000 IU twice daily	56	IV colistin	56	3	None	Cured
20 [15]	2100/ND	69	40	+	CSF	PDR	300 000 IU twice daily	21	None	–	1	None	Cured
21 [16]	130/68	36	136	ND	CSF	MDR	40 000 IU twice daily	17	Amphicillin–Sulbacin	ND	23	None	Cured
22 [17]	ND	ND	ND	ND	CSF	MDR	20 doses	ND	None	–	Sterile	None	Cured
23 [18]	3050/ND	ND	ND	+	CSF, B	PDR	125 000 IU twice daily	21	None	–	2	None	Cured
24 [19]	ND	ND	ND	ND	CSF	MDR	40 000 IU twice daily	42	IVT amikacin	42	Sterile	None	Cured

B, blood; CFP-S, cefoperazone–sulbactam; CIP, ciprofloxacin; CSF, cerebrospinal fluid; CV, chemical ventriculitis; EVDT, external ventricular drain tip; GS, Gram stain; IT, intrathecal; IV, intravenous; IVT, intraventricular; MDR, multidrug-resistant strain; N, neutrophil; ND, no data; PDR, pandrug-resistant strain; PF, peritoneal fluid; WBC, white blood cell.
[a]Duration from the day of IT/IVT colistin initiation to the first day of negative CSF culture.
[b]Death from myocardial infarction.
[c]Death from cardiac arrest.

aminoglycosides (amikacin and tobramycin), four (31%) received colistin, two (15%) received imipenem, two (15%) received cefoperazone-sulbactam, one (8%) received ciprofloxacin, and one (8%) received ampicillin–sulbactam.

IT/IVT colistin was added to the IV antibiotic regimens because of treatment failure in 11 (85%) of the 13 patients vs. concurrent initiation of these IV antibiotics in two patients (15%). The median duration from initiation of therapy to CSF sterilization was 3 days (range 1–23 days). Only ten participants (seven from our case series and three from the literature review) underwent IMD removal at the time of diagnosis, whereas there was no detailed information regarding IMD removal in the other reported cases. Overall clinical and microbiological cure rates with IT/IVT colistin therapy were 83% and 92%, respectively (Table 2). Three (13%) patients developed chemical ventriculitis and one (4%) developed dose-related seizures attributed to IT/IVT colistin. There was no case of nephrotoxicity, other AEs to colistin, or recurrent infection.

Predictors of mortality

There were no differences between nonsurvival and survival groups with respect to demographic factors, risk factors for *A. baumannii* acquisition, underlying conditions, clinical

TABLE 3. Clinical and microbiological cure rates of intrathecal (IT)/intraventricular (IVT) colistin monotherapy or in combination with systemic antibiotics for treatment of drug-resistant *Acinetobacter baumannii* meningitis

Regimens	References	Number of patients	Colistin dose[a] (duration)	Concurrent systemic antibiotics	Clinical cure rates[b] (%)	Microbiological cure rates[c] (%)
IT/IVT colistin monotherapy	Present study, 12, 13, 15, 18	11	40 000–400 000 IU/day (14–28 days)	None	10/11 (91)	10/11 (91)
Combined IT/IVT colistin and systemic antibiotics	Present study, 9, 11, 14, 16	13	40 000–500 000 IU/day (14–56 days)	Ampicillin–sulbactam Cefoperazone–sulbactam Amikacin Tobramycin Imipenem Colistin Cefoperazone-sulbactam + ciprofloxacin Colistin and amikacin	10/13 (77)	12/13 (92)

[a]Dose units were all converted to IU. Colistin 1 mg equals colistin 30 000 IU and colistimethate 1 mg equals colistin 12 500 IU.
[b]Rates of resolution of signs and symptoms of CNS infection, no subsequent need for additional antimicrobial therapy, and survival until hospital discharge.
[c]Rates of eradication of *A. baumannnii* in subsequent cultures.

presentations or CSF profiles. Patients who died had significantly higher APACHE II scores (mean score, 20 vs. 15; p 0.003) and received IT/IVT colistin therapy later (mean time from diagnosis to IT/IVT colistin therapy initiation, 7 vs. 2 days; p 0.01) than those who survived (Table 4). In multivariate analysis, the severity of illness, defined as APACHE score above 19, was the sole predictor of mortality (adjusted OR 49.5; 95% CI 1.7–1428.6; p 0.02) (Table 5).

TABLE 4. Factors associated with crude mortality among patients with multidrug-resistant (MDR) and pandrug-resistant *Acinetobacter baumannii* meningitis

Characteristics	Nonsurvival (*n* = 4)	Survival (*n* = 20)	p value
Age (years): mean (range)	52 (16–74)	35 (4–64)	0.08
Male sex	3 (75)	7 (35)	0.31
Underlying medical diseases[a]	3 (75)	6 (30)	0.58
CNS diseases			
Trauma/bleeding	2 (50)	15 (75)	0.55
Tumors	2 (50)	5 (25)	0.55
Clinical presentations			
Onset[b], mean days (range)	16 (8–30)	24 (4–82)	0.50
Fever	3 (75)	13 (65)	0.41
Headache	2 (50)	5 (25)	1.00
Mental status change	1 (25)	8 (40)	0.60
Seizure	0 (0)	2 (10)	1.00
Hypotension	1 (25)	2 (10)	1.00
Positive blood culture	0 (0)	3 (15)	1.00
APACHE II score, mean	20 (18–22)	15 (12–22)	**0.003**
PDR *A. baumannii* meningitis	2 (50)	11 (55)	1.00
Receipt of inadequate antimicrobial therapy[c]	4 (100)	10 (50)	0.53
Time to IT/IVT colistin initiation[d], mean days (range)	7 (3—15)	2 (0–6)	**0.01**
IT/IVT colistin therapy			
Use as monotherapy	1 (25)	11 (55)	0.59
Dose ≥ 125 000 IU/day	4 (100)	14 (70)	0.54
Duration, mean days (range)	11 (2–19)	19 (3–56)	0.24
Concurrent non-active IV antibiotics	1 (25)	5 (25)	1.00

Data are *n* (%) of patients, unless otherwise indicated.
APACHE-II, Acute Physiology and Chronic Health Evaluation II; CNS, central nervous system; IT, intrathecal; IV, intravenous; IVT, intraventricular; NS, nonsignificant.
Bold values signify statistical significance ($p < 0.05$).
[a]Include hypertension, alcoholism, chronic obstructive pulmonary diseases, diabetes mellitus, solid tumors, peritonitis, urinary tract infection, anorectal ulcers and *Pseudomonas aeruginosa* meningitis.
[b]Duration from the day of admission to the onset of meningitis.
[c]Delay of receipt of appropriate antibiotic therapy within 48 h after the positive cerebrospinal fluid culture or receipt of antibiotics that did not have efficacy against the isolated microorganisms [34].
[d]Duration from the day of meningitis diagnosis to the day of IT/IVT colistin therapy initiation.

Discussion

A. baumannii is typically a healthcare-associated pathogen associated with a wide range of infections [1,3]. Notably, post-neurosurgical MDR *A. baumanii* meningitis increased from 0% during 1986–1993 to 8% during 1994–2001 in Taiwan [24]. The findings of the present study highlight seven cases of PDR *A. baumannii* infections from a Thai hospital between the years 2004–2008 and 17 reported cases in the literature with a mixture of MDR and PDR *A. baumannii* phenotypes. Fifteen of the 17 (88%) cases from the literature review were reported in the past decade, implicating an increase in incidence of drug-resistant *A. baumannii* CNS infection coincident with acquisition of resistance genes, a rise in the proportion and longevity of critically-ill patients, advances in medicine, and selective pressures of broad-spectrum antibiotic use [8,25].

Given the emergence of *A. baumanni* resistance to most antibiotic classes, carbapenems alone or in combination with aminoglycosides became the reference standard for empirical treatment in cases of suspected MDR *A. baumannii* infection [2,8]. The emergence of carbapenem-resistant and PDR *A. baumannii* strains now suggests that this historical approach to empirical treatment of infections caused by the versatile pathogen needs to be reassessed [1–4,8,25]. In one retrospective study that compared colistin monotherapy to

Table 5. Multivariate logistic regression analysis for predictors of death among patients with multidrug- and pandrug-resistant *Acinetobacter baumannii* central nervous system infections

Variables	Adjusted odds ratio (95% CI)	p value
APACHE II scores > 19[a]	49.5 (1.7–1428.6)	0.02
Age ≥ 45 years old	10.5 (0.9–92.4)	0.08
IT/IVT colistin therapy initiated >48 h from diagnosis	6.8 (0.7–60.9)	0.10

IT/IVT, intrathecal/intraventricular.
[a]APACHE II score > 19 and receipt of inadequate antimicrobial therapy were covariated. Only APACHE II scores > 19 were selected in the multivariate model.

colistin plus meropenem in humans, there was significantly higher survival in patients treated with colistin alone, whereas there were similar rates of nephrotoxicity [26]. In our review, there were no significant differences in cure rates between IT/IVT colistin monotherapy and combination therapy with IT/IVT colistin and other IV antibiotics (Table 3). Because most of the concurrent IV antibiotics (85%) had failed in the treatment of the infection prior to IT/IVT colistin therapy, these cure rates likely represent the effect of IT/IVT colistin therapy rather than that of the IV antibiotics.

Interest in refined colistin use waned in the early 1980s and pharmacokinetic and pharmocodynamic data for colistin are limited. In one study, 25% of the serum concentration of colistin was detected in CSF and bactericidal activity was sustained [27]. In 1990, IT/IVT colistin therapy was first reported, yet the optimal dose and duration of therapy remains undetermined given only anecdotal use in a small number of reported cases [2,9–19,27]. According to our review, the clinical and microbiological cure rates were above 80%, and the commonly administered dose, based on our experience and other reports, was 40 000–500 000 IU/day (1 mg of colistin equals 30 000 IU of colistin and 1 mg of colistimethate equals 12 500 IU of colistin), mixed with 0.9% sodium chloride, given once or twice daily through a ventricular catheter or a spinal needle after an equivalent volume of CSF was extracted. For patients with an external ventricular drain, the drainage was interrupted for 2 h. Duration of therapy was in a range of 2–3 weeks but may have varied depending on clinical response, with sterilization of the CSF expected within 72 h.

The present study demonstrated that high APACHE II score (>19) and delayed IT/IVT colistin therapy were associated with mortality. Other reported predictors of mortality included advanced age, high CSF leukocyte counts, carbapenemase-producing isolates and receipt of inadequate therapy [2]. As noted in other studies, early IMD removal has been associated with survival and should be performed, if feasible, in conjunction with antimicrobial therapy [2]. However, despite of our small sample size and the best available data from the literature review, we could not assess the impact of IMD removal on mortality in the present study.

Colistin treatment regimens were replaced by regimens with other antibiotics in the 1970s because of nephrotoxicity and neurotoxicity [28]. However, the incidence of IV colistin-related nephrotoxicity reportedly decreased from 36% in the 1960s to 14–19% in the period of 1990–2000, and significant neurotoxicity attributed to IV colistin has been rare in the past 15 years [28]. These lower rates of colistin-related adverse effects (AEs) may be the result of a combination of the less toxic colistimethate, more meticulous management of fluid and electrolytes, heightened recognition of colistin toxicities, and close monitoring of the AEs in clinical practice. In our review, seizures and chemical ventriculitis were associated with IVT/IT colistin therapy, yet it was continued and clinical recovery was achieved in these cases without sequelae from the AEs [9,13].

We acknowledge some notable limitations of the present study. First, the design had an inherent bias as a result of the identification of cases from a literature review that undoubtedly reflects publication and information biases. Some data (responses) were missing from both the retrospective chart review and published case reports. Hence, we attempted to minimize information biases and misclassification biases using standardized data-gathering instruments and calculation of the APACHE II score at the same point of time. Second, although the severity of illness (APACHE II score) is usually calculated at the time of admission, a recent study suggested that the optimal time to measure the severity is 24 h before collection of the first culture-positive sample [20], which is what we did in this study. The reason is that this time point is close to the onset of infection and therefore may represent a better comparative criterion for study participants [20]. Third, the small number of reported cases of MDR/PDR *A. baumannii* limited our ability to detect other potential factors associated with mortality (e.g. age and IT/IVT colistin therapy initiated >48 h after diagnosis). Fourth, our study cohort represents a large number of cases (29%) from our Thai hospital site and hence the data obtained from this study population may not be generalized to other populations. Lastly, in two patients in whom treatment failure was documented microbiologically, no colistin MIC data were available and the causes of death were not clearly described. The emergence of *A. baumannii* resistance to colistin remains a potential cause of treatment failure and mortality in such cases.

In conclusion, the findings obtained in the present study suggest that IT/IVT colistin therapy is efficacious as either primary or adjunct treatment of MDR or PDR *A. baumannii* CNS infection. Our findings contribute to an enhanced understanding concerning the clinical manifestations of this virulent and versatile, drug-resistant pathogen. Larger observational studies, if not randomized trials, are needed to assess the optimal dosage, duration, pharmacokinetic/pharmacodynamic parameters, effectiveness, and AEs associated with IT/IVT colistin when used as monotherapy or in combination with other systemic antibiotics for this CNS infection.

Transparency Declaration

All authors have no conflict of interest pertaining to this study. L. M. Mundy is a consultant to the Department of WWEpidemiology at GlaxoSmithKline, Inc.

References

1. Abbo A, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, Carmeli Y. Multidrug-resistant *Acinetobacter baumannii*. *Emerg Infect Dis* 2005; 11: 22–29.
2. Rodríguez Guardado A, Blanco A, Asensi V *et al.* Multidrug-resistant *Acinetobacter meningitis* in neurosurgical patients with intraventricular catheters: assessment of different treatments. *J Antimicrob Chemother* 2008; 61: 908–913.
3. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis* 2008; 46: 1254–1263.
4. Murray CK, Hospenthal DR. Treatment of multidrug resistant *Acinetobacter*. *Curr Opin Infect Dis* 2005; 18: 502–506.
5. Andes DR, Craig WA. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect Dis Clin North Am* 1999; 13: 595–618.
6. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann Intern Med* 1970; 72: 857–868.
7. Rose WE, Rybak MJ. Tigecycline: first of a new class of antimicrobial agents. *Pharmacotherapy* 2006; 26: 1099–1110.
8. Gilad J, Carmeli Y. Treatment options for multidrug-resistant *Acinetobacter* species. *Drugs* 2008; 68: 165–189.
9. Ng J, Gosbell IB, Kelly JA, Boyle MJ, Ferguson JK. Cure of multiresistant *Acinetobacter baumannii* central nervous system infections with intraventricular or intrathecal colistin: case series and literature review. *J Antimicrob Chemother* 2006; 58: 1078–1081.
10. Berlana D, Llop JM, Fort E, Badia MB, Jódar R. Use of colistin in the treatment of multiple-drug-resistant Gram-negative infections. *Am J Health Syst Pharm* 2005; 62: 39–47.
11. Fernandez-Viladrich P, Corbella X, Corral L, Tubau F, Mateu A. Successful treatment of ventriculitis due to carbapenem-resistant *Acinetobacter baumannii* with intraventricular colistin sulfomethate sodium. *Clin Infect Dis* 1999; 28: 916–917.
12. Al Shirawi N, Memish ZA, Cherfan A, Al Shimemeri A. Post-neurosurgical meningitis due to multidrug-resistant *Acinetobacter baumanii* treated with intrathecal colistin: case report and review of the literature. *J Chemother* 2006; 18: 554–558.
13. Sueke H, Marsh H, Dhital A. Using intrathecal colistin for multidrug resistant shunt infection. *Br J Neurosurg* 2005; 19: 51–52.
14. Ho YH, Wang LS, Chao HJ, Chang KC, Su CF. Successful treatment of meningitis caused by multidrug-resistant *Acinetobacter baumannii* with intravenous and intrathecal colistin. *J Microbiol Immunol Infect* 2007; 40: 537–540.
15. Vasen W, Desmery P, Ilutovich S, Di Martino A. Intrathecal use of colistin. *J Clin Microbiol* 2000; 38: 3523.
16. Benifla M, Zucker G, Cohen A, Alkan M. Successful treatment of *Acinetobacter meningitis* with intrathecal polymyxin E. *J Antimicrob Chemother* 2004; 54: 290–292.
17. Kaplan SL, Patrick CC. Cefotaxime and aminoglycoside treatment of meningitis caused by Gram-negative enteric organisms. *Pediatr Infect Dis J* 1990; 9: 810–814.
18. Bukhary Z, Mahmood W, Al-Khani A, Al-Abdely HM. Treatment of nosocomial meningitis due to a multidrug resistant *Acinetobacter baumannii* with intraventricular colistin. *Saudi Med J* 2005; 26: 656–658.
19. Kasiakou SK, Rafailidis PI, Liaropoulos K, Falagas ME. Cure of post-traumatic recurrent multiresistant Gram-negative rod meningitis with intraventricular colistin. *J Infect* 2005; 50: 348–352.
20. Thom KA, Shardell MD, Osih RB *et al.* Controlling for severity of illness in outcome studies involving infectious diseases: impact of measurement at different time points. *Infect Control Hosp Epidemiol* 2008; 29: 1048–1053.
21. Clinical and Laboratory Standard Institute (CLSI). *Performance standards for antimicrobial susceptibility testing: seventeenth informational supplement*. Wayne, PA: CLSI, 2007: M100-S17.
22. Apisarnthanarak A, Pinitchai U, Thongphubeth K *et al.* A multifaceted intervention to reduce pandrug-resistant *Acinetobacter baumannii* colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study. *Clin Infect Dis* 2008; 47: 760–767.
23. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 2000; 31 (suppl): 131–138.
24. Wang KW, Chang WN, Huang CR *et al.* Post-neurosurgical nosocomial bacterial meningitis in adults: microbiology, clinical features, and outcomes. *J Clin Neurosci* 2005; 12: 647–650.
25. Adams MD, Goglin K, Molyneaux N *et al.* Comparative genome sequence analysis of multidrug-resistant *Acinetobacter baumannii*. *J Bacteriol* 2008; 190: 8053–8064.
26. Falagas ME, Rafailidis PI, Kasiakou SK, Hatzopoulou P, Michalopoulos A. Effectiveness and nephrotoxicity of colistin monotherapy vs. colistin-meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. *Clin Microbiol Infect* 2006; 12: 1227–1230.
27. Jiménez-Mejías ME, Pichardo-Guerrero C, Márquez-Rivas FJ, Martín-Lozano D, Prados T, Pachón J. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant *Acinetobacter baumannii* meningitis. *Eur J Clin Microbiol Infect Dis* 2002; 21: 212–214.
28. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006; 10: R27.