The 21st-century challenge to neurocritical care: the rise of the superbug *Acinetobacter baumannii*. A meta-analysis of the role of intrathecal or intraventricular antimicrobial therapy in reduction of mortality

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OBJECTIVE Neurosurgical infections due to multidrug-resistant organisms have become a nightmare that neurosurgeons are facing in the 21st century. This is the dawn of the so-called postantibiotic era. There is an urgent need to review and evaluate ways to reduce the high mortality rates due to these infections. The present study evaluates the efficacy of combined intravenous plus intrathecal or intraventricular (IV + IT) therapy versus only intravenous (IV) therapy in treating postneurosurgical *Acinetobacter baumannii* infections.

METHODS The authors performed a meta-analysis of all peer-reviewed studies from the PubMed, Cochrane Library database, ScienceDirect, and EMBASE in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Five studies were finally included in the present analysis: 126 patients were studied who had postneurosurgical *A. baumannii* infection. The Cochrane collaboration tool was used to evaluate risk of bias, and a test of heterogeneity was performed. The I^2 statistic was calculated. The patients were divided into 2 groups: the IV group received only intravenous therapy and the IV + IT group received both intravenous and intrathecal or intraventricular antimicrobial therapy. The outcome was mortality attributed specifically to *A. baumannii* infection in postneurosurgical cases. The pooled data were analyzed using the Cochran-Mantel-Haenszel method in a fixed-effects model.

RESULTS The total number of patients in the IV-only group was 73, and the number of patients in the IV + IT group was 53. The mean duration of intravenous therapy was 27 days. The mean duration of intrathecal colistin was 21 days. The intravenous dose of colistin ranged from 3.75 to 8.8 MIU per day. The dose of intrathecal colistin ranged between 125,000 and 250,000 IU per day. The overall calculated odds ratio for mortality for the IV + IT group after pooling the data was 0.16 (95% CI 0.06–0.40, $p < 0.0001$). The patients who received IV + IT therapy had an 84% lower risk of dying due to the infection compared with those who received only IV therapy.

CONCLUSIONS There is an 84% lower risk of mortality in patients who have been treated with combined intrathecal or intraventricular plus intravenous antimicrobial therapy versus those who have been treated with intravenous therapy alone. The intrathecal or intraventricular route should be strongly considered when dealing with postneurosurgical multidrug-resistant *A. baumannii* infections.

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KEY WORDS *Acinetobacter baumannii*; multidrug resistance; intraventricular; intrathecal; postoperative neurosurgical infection; colistin

POSTNEUROSURGICAL infections due to multidrug-resistant (MDR) organisms have become a nightmare for 21st-century neurosurgeons. This period has already been called the dawn of the postantibiotic era.²¹ The accidental discovery of penicillin by Sir Alexander Fleming

heralded the era of antibiotics and of human dominance over pathogens. Approximately 1 century later, at least in critical care settings, the pathogens seem to be dominating again. *Acinetobacter baumannii* is one such pathogen that has become the scourge of neurosurgical ICUs worldwide,

ABBREVIATIONS CMS = colistimethate sodium; IV + IT = intravenous plus intrathecal or intraventricular; MDR = multidrug-resistant; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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resulting in several global outbreaks.²⁷ The mortality rate due to MDR *A. baumannii* meningitis can range from 15% to 72.7%.^{17,21,26}

The data from SENTRY (Antimicrobial Surveillance Program), MYSTIC (Meropenem Yearly Susceptibility Test Information Collection), and other sources have reported the emergence of MDR *A. baumannii* from Europe, North America, Argentina, Brazil, China, Taiwan, Hong Kong, Japan, Korea, and even remote islands like Tahiti.²¹ It has been nicknamed “Iraqibacter” due to the increased number of nosocomial infections in military hospitals during Operation Iraqi Freedom.¹ In this evolutionary arms race, there is an urgent need to review, evaluate, and find new ways to tackle this difficult problem. The intrathecal or intraventricular (IT) administration of antibiotics has been tried as a last resort in many cases of severe neuro-infections not responding to traditional intravenous (IV) regimens.¹⁰ This analysis is an attempt to review the role of intrathecal or intraventricular antibiotic therapy and its effect on the mortality rate.

Methods

The aim of the study was to review the benefit of combined IV + IT therapy over exclusive IV therapy. The outcome studied was mortality attributed specifically to *A. baumannii* meningitis. A detailed protocol about the literature search, inclusion and exclusion criteria, selection of cases, and statistical methodology was developed. The guidelines laid out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed. Two investigators (N.M. and V.N.) performed the literature search. To minimize selection bias, 2 reviewers (A.S. and D.P.) reviewed the articles independently. In case of doubt, a mutual consensus was reached after discussion.

Literature Search Strategy

A computerized search of titles and abstracts from January 1960 to May 2017 was performed in PubMed, Cochrane Library database, ScienceDirect, and EMBASE. A combination of key word searches was made to build a search strategy. The non-English articles were also searched. Two non-English articles were reviewed after translation. An independent Web search was made with the key words to include any unpublished literature. The reference lists of final selected articles were examined and reviewed (Fig. 1). Key words that were used to build the search directory were “*Acinetobacter baumannii*,” “Neurosurgery,” “postoperative,” and “infections.” The example of a PubMed search directory is as follows: (“*acinetobacter baumannii*”[MeSH Terms]) OR (“*acinetobacter*”[All Fields] AND “*baumannii*”[All Fields]) OR “*acinetobacter baumannii*”[All Fields]) AND (“neurosurgical procedures”[MeSH Terms] OR (“neurosurgical”[All Fields] AND “procedures”[All Fields]) OR “neurosurgical procedures”[All Fields] OR “neurosurgery”[All Fields] OR “neurosurgery”[MeSH Terms]). Additional search terms used were “intrathecal,” “intraventricular,” “colistin,” “polymyxin,” “meningitis,” “craniotomy,” and “multidrug resistant.”

Risk of Bias Assessment

Two investigators independently reviewed all the articles to eliminate selection bias. Disagreements were sorted out after discussing the merit of each study. The heterogeneity of the selected studies was assessed with the I^2 statistic. The I^2 value of the present study was 28%. A funnel plot was charted to evaluate bias.

Inclusion and Exclusion Criteria

Patients who had undergone any neurosurgical procedure of the brain and spine and who subsequently developed CNS infection with *A. baumannii* in the postoperative period were considered. Only the studies that had comparative cohorts of patients undergoing IV and IV + IT therapy were selected. The studies with incomplete data about treatment and outcome were excluded, and the case reports were excluded. The groups were matched for their similarities to remove confounding variables. Postoperative meningitis was defined according to the Centers for Disease Control’s definition. Infection was positive if at least 1 of the following 2 criteria was fulfilled: 1) the isolation of *Acinetobacter* from the CSF; and 2) fever > 38°C in the absence of any other recognizable cause—with any of the following: increased leukocyte count > 10/mm³ with > 50% polymorphs; increased protein (> 45 mg/dl) in CSF; and/or decreased levels of glucose (< 40 mg/dl) in CSF. A positive culture from CSF without clinical symptoms and normal results on CSF analysis was not considered an infection. Therapeutic cure was defined as resolution of signs and symptoms, with clinical improvement and no growth in 2 successive CSF cultures.

Statistical Analysis

The test for heterogeneity was performed and the I^2 value evaluated. The data were analyzed with the fixed-effects model due to acceptable heterogeneity. The odds ratios with the respective confidence intervals were calculated for each study. The Cochran-Mantel-Haenszel method was used to generate an estimate of an association between the study groups. The data type was dichotomous and was expressed as an odds ratio with 95% confidence interval. A forest plot was charted and analyzed. The overall odds ratio and risk estimation was then made by summarizing all the studies. The studies were weighted according to their sample sizes. Statistical analysis was done using the Review Manager computer program (RevMan version 5.3; Copenhagen: Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

Results

Five studies with 126 patients were selected (Table 1). All patients had undergone a neurosurgical procedure or procedures and had tested positive for infection with *A. baumannii*. The selected studies were matched to evaluate homogeneity. The test for homogeneity was performed, and the I^2 value was 28% (Fig. 2). The 2 groups were called “IV” for the patients who received intravenous antibiotics only, and “IV + IT” for those who received intravenous and intrathecal antibiotics. The total number of patients in the IV-only group was 73, and the number of patients

FIG. 1. The PRISMA flow diagram of systematic literature search.

in the IV + IT group was 53. The mean age in the study cohort was 48.8 years. The male/female ratio was 2.1. The underlying disease was traumatic brain injury in 35 cases, intracerebral bleed in 56 cases, and brain neoplasm in 20 cases. The intravenous dose of colistin ranged from 3.75 to 8.8 MIU per day, and the mean duration of IV therapy was 27 days. The dose of intrathecal colistin ranged from 125,000 to 250,000 IU per day, and the mean duration of intrathecal colistin was 21 days (Table 2).

The data from all the subgroups in the 5 studies were analyzed by the Cochran-Mantel-Haenszel method and charted in a forest plot (Fig. 3). The overall calculated odds ratio for mortality after pooling all the data was 0.16 (95% CI 0.06–0.40, $p < 0.0001$) for the IV + IT group. The patients who received IV + IT therapy had an 84% lower risk of dying due to infection compared with those who received only IV therapy. This is a very significant risk reduction for the cohorts that received IV + IT therapy.

Discussion

Acinetobacter baumannii (from the Greek word “akinetos,” meaning nonmotile) was first isolated by the

Dutch microbiologist Beijerinck in 1911 from soil, as described in Antunes et al.² From its low profile of an opportunistic organism with low virulence,²⁰ it has shot into prominence as one of the foremost concerns of the critical care community today.

“Multidrug resistance” in literal terms means resistance to < 1 antimicrobial agent. The scientific definition is “resistance to three or more anti-microbial classes.”¹⁵ The antimicrobial resistance of *A. baumannii* significantly increased worldwide between 2004 and 2009.¹² The evolution of carbapenem-resistant *A. baumannii* has been the most worrying trend. Imipenem resistance in *A. baumannii* has reached $> 50\%$ from a worldwide collection between 2005 and 2009. The once-discarded antibiotics have found new relevance in this context. The most important among them in the fight with *A. baumannii* is colistin, also known as polymyxin E, which is an antibiotic produced by some strains of the bacterium *Paenibacillus polymyxa*. Structurally they are cyclic polypeptides.⁶ Colistin is given in the form of colistimethate sodium (CMS), which has fewer adverse reactions than colistin.

The pharmacokinetics of drug entry into the CNS is a

TABLE 1. Details of the patients included in the meta-analysis of MDR *A. baumannii*

Variable	Fotakopoulos et al., 2016*	De Bonis et al., 2016	Tuon et al., 2010	Rodriguez et al., 2008	Moon et al., 2013
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	24	18	19†	46	21
Mean age in yrs (range)	49	52.05	43 (21–91)	44 (15–78)	56 (20–83)
Sex, M/F	13/11	10/8	12/7	34/12	15/6
Diagnosis					
TBI	15 (62.5%)	2 (11.1%)	4 (21%)	11 (25.5%)	3 (13.6%)
SAH	NA	2 (11.1%)	NA	NA	NA
ICH	16 (66.6%)	5 (27.7%)	NA	23 (51%)	12 (54.5%)
Brain tumors	3 (12.5%)	4 (22.2%)		10 (23%)	3 (13.6%)
No. of EVDs	NA	6	12	NA	15
VPS	NA	4 (22.2%)		NA	4
Intrathecal or intraventricular dose of colistin, IU $\times 10^3$	170 $\pm$ 0.4	125–250	NA	NA	125
Duration of IT dose in days	16.0 $\pm$ 8.3	26 (14–40)	NA	NA	NA
IV dose of colistin, IU $\times 10^6$	8.8 $\pm$ 0.1	NA	NA	NA	3.75
Duration of IV dose in days	16.0 $\pm$ 8.3	NA	NA	17	NA

EVD = external ventricular drain; ICH = intracerebral hemorrhage; NA = not available; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; VPS = ventriculo-peritoneal shunt.

* Data on doses are expressed as the mean $\pm$ SD.

† Two patients were not included in the statistical analysis due to reported contamination and/or colonization.

complex process. It depends on the molecular size, electric charge, lipid solubility, plasma protein binding ability, the affinity to the active transport system, CSF flow, and meningeal inflammation.¹⁹ There is a wide variation from one patient to another in the CSF concentration of the drug, despite giving the same dosage. James et al. found that the concentration of drug in CSF in patients receiving the maximum dosage of intravenous antibiot-

ics alone was for the most part ≤ 5 $\mu\text{g/ml}$ and > 5 $\mu\text{g/ml}$ for drugs given by the intraventricular route.⁸ The colistin penetration into CSF may be as low as 5%¹⁶ to 25%.⁸ The poor penetration into CSF may be the reason for very high mortality rates in the subgroup not receiving intrathecal therapy. The risk of nephrotoxicity with polymyxin therapy ranges from 10% to 18%.⁶ There is a substantial risk of nephrotoxicity with use of colistin that

FIG. 2. Funnel plot showing the distribution of studies for assessment of bias. SE = standard error.

TABLE 2. Mortality rates in different subgroups of patients with MDR *A. baumannii*

Group	Fotakopoulos et al., 2016	De Bonis et al., 2016	Tuon et al., 2010	Rodriguez et al., 2008	Moon et al., 2013
IV group					
No. of patients	9	9	15	29	11
No. of deaths	8	5	13	11	4
IV + IT group					
No. of patients	15	9	2	17	10
No. of deaths	2	0	2	2	2
Time to CSF sterilization in days	NA	21 (8–48)	NA	21	NA
Overall mortality, no. (%)	10 (41.6)	5 (27.7)	15 (78)	13 (28.2)	6 (28.5)

may require dosage reduction and further jeopardize the outcome of treatment.⁵ This drug has also been linked to neurotoxicity. Polymyxins can cause neuromuscular blockade due to inhibition of acetylcholine release. The majority of postneurosurgical *A. baumannii* infections are associated with indwelling ventriculostomy tubes or CSF leaks.²⁴ The median time for development of postoperative meningitis is 12 days (range 1–40 days). The risk factors predisposing patients to postneurosurgical *A. baumannii* meningitis are CSF leaks,¹¹ prolonged external ventricular drainage,¹² prolonged duration of surgery,¹¹ opening of sinus during surgery,¹² wound infection,¹¹ repeat surgery,²² and critical illness.¹²

The 2017 Infectious Diseases Society of America's guidelines²⁵ state that intraventricular antimicrobial therapy should be considered in patients with health care–associated meningitis who respond poorly to systemic therapy. It is also recommended to clamp the ventricular or intrathecal drain for a period of 15–60 minutes to allow the drug to achieve an equilibrium. The actual intraventricular dosage is determined by calculating the “inhibitory quotient.” After administering the first dose, the trough levels of antibiotic are determined from the sample of CSF taken just before giving the second dose. The inhibitory quotient is calculated by dividing the trough level by the minimum inhibitory concentration for the organism. The inhibitory quotient should exceed 10–20 for consistent CSF sterilization. The dosage also needs adjustment depending on the size of the ventricle and daily output from the drain. For

the infected CSF drain or shunt tube, removal is recommended.

The recommended doses of colistin for intraventricular administration are 5 mg or 62,500 IU per day (1 mg of CMS = 12,500 IU) in adults and 2 mg or 25,000 IU per day in children.²⁵ The recommended pediatric dosage of CMS per day is between 50,000 and 75,000 IU/kg/day (4–6 mg/kg of body weight/day) in Europe and 83,000–166,000 IU/kg/day (6.6–13.3 mg/kg/day) in the US.¹³ The British Society for Antimicrobial Chemotherapy Working Party recommended that the initial intraventricular dose should be based on the ventricular volume as determined by imaging.³ To avoid increasing intracranial pressure before drug instillation, an equal volume of CSF must be removed. After instillation of the drug, a saline flush is done to minimize the amount of drug left over in the drain tube. The patient's neurological status must be monitored both before and after giving the drug via the intraventricular route.

De Bonis et al.⁴ reported a CSF sterilization rate of 33% in the IV-only group and 100% in the IV + IT group ($p = 0.009$). The mean time for CSF sterilization was 21 days. Tuon et al.²⁶ reported a high mortality rate of 72.7%. Only 2 patients in their study received intrathecal therapy. Two patients who received IV + IT therapy also died. It is interesting to note that only 69% of patients who died received appropriate, sensitive antibiotics. Thus, an inappropriate antibiotic regimen could have led to the ineffectiveness of IV + IT therapy in this study. Transmission of infec-

FIG. 3. Forest plot with mortality as the outcome showing the calculated odds ratios, weights, and confidence interval of each study, and the overall pooled odds ratio. The event here is the number of deaths that have occurred in the respective groups. M-H = Mantel-Haenszel.

tion from other sources like the lungs and urinary tract is a concern in the ICU setting. Fotakopoulos et al.⁷ found that 5.6% of external ventricular drains were infected with *A. baumannii*.

The importance of strict adherence to hand hygiene and hospital infection protocols cannot be overemphasized. It must be remembered that starting IV + IT therapy does not guarantee the survival of patients. In the studies reviewed, 8 deaths occurred in IV + IT group. What has caused the deaths in these cases? This could be explained in part due to late initiation of intraventricular therapy. It must be inferred that in usual clinical practice, IV therapy is started first, and when there is no improvement, then as a last resort IV + IT therapy is started. We challenge this notion and hypothesize that this may lead to worse outcomes. The other reason could be the variation in the sensitivity patterns of the organism to the antibiotics. Moon et al.¹⁸ found that carbapenem-resistant strains had a higher mortality than other strains. It is not possible to answer this question based on the current study; randomized controlled trials are needed to address these issues. In the absence of clear guidelines, clinicians are faced with a difficult dilemma in caring for these patients. In the situation of clinical nonimprovement with systemic therapy, it is prudent to get intrathecal or intraventricular access and commence the therapy at the earliest possible time. If sensitivity is demonstrated only for colistin, then we recommend that IV + IT therapy be started at the earliest opportunity.

Limitations of the Study

Our study has limitations in evaluating a small number of observational studies, the results of all of which are in favor of IV + IT therapy. However, all the studies have limited sample size, with considerable variability in the mortality rates. Hence, we felt a need to assess the overall impact of IV + IT therapy on the mortality rate in a larger cohort, and to establish its unequivocal role in reducing mortality. Further questions like optimum intraventricular dosage, duration of the treatment, and the treatment strategy in pan-drug-resistant infections need serious attention.

Conclusions

The data analyzed from this study show that the inclusion of intrathecal or intraventricular antimicrobial therapy with intravenous therapy is associated with an 84% lower chance of mortality in postneurosurgical infections due to *A. baumannii*. The intrathecal route should be strongly considered when dealing with postneurosurgical *A. baumannii* infections.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Nanda, Mohammed, Savardekar. Acquisition of data: Mohammed, Narayan. Analysis and interpretation of data: Mohammed. Drafting the article: Mohammed, Savardekar, Patra, Narayan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nanda. Statistical analysis: Mohammed, Narayan. Administrative/technical/material support: Nanda, Savardekar, Patra. Study supervision: Nanda.

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