Lower respiratory tract infections due to multi-drug resistant pathogens in central nervous system injuries (Review)

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Abstract. Pneumonia is one of the most prevalent infections in the intensive care unit (ICU), where pneumonia may occur during hospitalization in the ICU as a complication. ICU patients with central nervous system (CNS) injuries are not an exception, and they may even be more susceptible to infections such as pneumonia due to issues such as swallowing difficulties, the requirement for mechanical ventilation, and extended hospital stay. Numerous common CNS injuries, such as ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage, can prolong hospital stay and increase the risk of pneumonia. Multidrug-resistant (MDR) microorganisms are a common and significant concern, with increased mortality in nosocomial pneumonia. However, research on pneumonia due to MDR pathogens in patients with CNS injuries is limited. The aim of the present review was to provide the current evidence regarding pneumonia due to MDR pathogens in patients with CNS injuries. The prevalence of pneumonia due to MDR pathogens in CNS injuries differs among different settings, types of CNS injuries, geographical areas, and time periods in which the studies were performed. Specific risk factors for the emergence of pneumonia due to MDR pathogens have been identified in ICUs and neurological rehabilitation units. Antimicrobial resistance is currently a global issue, although using preventive measures, early diagnosis, and close monitoring of MDR strains may lessen its impact. Since there is a lack of information on these topics, more multicenter prospective studies are required to offer insights into the clinical features and outcomes of these patients.

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1. Introduction

Nosocomial or hospital-acquired pneumonia (HAP) is an infection that appears during a hospital stay, usually 48 h or more after being admitted or within 14 days of discharge and was either absent or not incubating at the time of admission (1). HAP is the second most frequent nosocomial infection following urinary tract infections, with an incidence of 15-20%, according to a study from the United States (2). It is one of the primary causes of mortality in intensive care unit (ICU) patients (accounting for 25-50% of deaths) (1) and one of the causes of fatal hospital infections (mortality rate, 13%). Mechanical ventilation for >48 h (HAP incidence, 9-40%), length of hospital stay (HAP incidence, 3.3% until day 5; 1.3%

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at day 15), severity of underlying disease, Acute Physiology and Chronic Health Evaluation (APACHE) score (3), and the presence of comorbidities are the most important risk factors (4).

Hospitalized patients with central nervous system (CNS) injuries are particularly vulnerable to pneumonia, which can be exacerbated by bed rest, dysphagia, mental instability, or mechanical ventilation brought on by weak respiratory muscles (5). Pneumonia is one of the most common respiratory complications in stroke patients, affecting 5 to 9% of patients (6,7), and is much commoner in patients admitted to neuro-ICUs, which are ICUs devoted to the care of patients with immediately life-threatening neurological problems (incidence, 13-33%) (8). Due to the long time spent in the prone position and the risk of inhaling stomach contents that comes with it, a large number of people (up to 60%) with serious brain injuries develop pneumonia (9).

Immune system dysregulation due to persistent inflammatory response and excessive sympathetic activation are involved in the pathogenesis of pneumonia in individuals with CNS injuries. More specifically, in CNS injuries, secondary brain tissue damage is caused by the acute immune response, which is followed by immunosuppression caused by sympathetic nervous system activation. The latter raises the risk of infectious complications such as pneumonia. The inflammatory state caused by pneumonia can trigger a bystander autoimmune response against CNS antigens, resulting in a vicious cycle (10).

Nosocomial pneumonia affects ~36% of patients hospitalized for >48 h in neuro-ICUs (11). Other common infections in neuro-ICUs are urinary tract infections, bacteremia, and intracranial infections such as ventriculitis and meningitis (11). These infections can affect patient outcomes and increase mortality rates in critically ill patients. In addition, these infections increase the costs placed on healthcare systems (12,13).

Among the most frequent types of infections in patients admitted to neuro-ICUs is ventilator-associated pneumonia (VAP), which appears in mechanically ventilated individuals at least 48 h after endotracheal intubation without any signs of a prior infection. It usually results from aspiration of oropharyngeal secretions into the tracheobronchial tree around the endotracheal cuff (14). Subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and stroke patients all require intensive care and may be admitted to neuro-ICUs, where they may be vulnerable to nosocomial infections such as pneumonia. Patients with subdural hematomas and intracerebral/intraventricular hemorrhages (IVH) have the greatest incidence rates of nosocomial infections, with rates of 21.3 and 21.1 cases per 1,000 days of hospitalization at the neuro-ICU, respectively (15).

Multidrug-resistant (MDR) microorganisms are defined as those that are resistant to at least one agent from three or more antimicrobial classes, including β-lactam/β-lactamase inhibitors; carbapenems; aminoglycosides; third- or fourth-generation cephalosporins, fluoroquinolones, and carbapenems for Gram-negative pathogens; non-susceptibility to oxacillin and/or cefoxitin (anti-staphylococcal β-lactams) for Gram-positive *Staphylococcus aureus* (*S. aureus*); and non-susceptibility to vancomycin and/or teicoplanin for Gram-positive *Enterococcus spp.* (16,17).

MDR microorganisms are a prevalent and serious concern with increased mortality in HAP and VAP (18). There is a scarcity of information on pneumonia due to MDR pathogens in patients with CNS injuries. The aim of the present review was to report the current evidence regarding pneumonia due to MDR pathogens in patients with CNS injuries.

2. Data extraction and synthesis

In order to provide insight regarding MDR pneumonia in patients with CNS injuries, an electronic search in PubMed and Google Scholar was performed with the keywords 'multi-drug resistant pneumonia' OR 'MDR pneumonia' OR 'multi-drug resistant respiratory infections' OR 'MDR respiratory infections' AND 'central nervous injuries' OR 'brain injuries' OR 'stroke' OR 'intracranial hemorrhage' OR 'subarachnoid hemorrhage' OR 'neurorehabilitation unit' OR 'neurointensive care unit' OR 'neurological disorders' OR 'neurological injuries', without language limitations in the selection of articles reporting data on MDR pneumonia in CNS injuries. Two authors thoroughly reviewed all articles. The reference list of each article that met the criteria was also hand-searched for other potentially relevant studies. Overall, 192 articles were found using the search criteria and the reference lists of previously identified documents. After eliminating duplicates, 119 were eliminated after title, abstract, or full text screening. Finally, nine articles presenting original studies providing data on MDR pneumonia in CNS injuries were included in data synthesis.

3. Mechanisms responsible for pneumonia development in CNS injuries

Critical illnesses of the CNS are more likely to result in pneumonia than in other illnesses in ICUs due to factors such as immunological dysregulation and immunosuppression resulting from brain injury, increased incidence of dysphagia, and the insertion of external ventricular drains (EVDs) (19). In patients with brain damage, immunological dysregulation is predominantly caused by a heightened inflammatory response that results in the production of chemokines, proinflammatory cytokines, and cell adhesion molecules both centrally and peripherally (20). These cytokines are produced to eliminate cellular debris in the CNS after injury, and an inflammatory response develops. However, a persistent and protracted inflammatory response can result in immune system dysregulation (21-23). More specifically, it has been found that three months after TBI, affected individuals frequently display extensive, densely packed, reactive microglia (CR3/43- and/or CD68-immunoreactive) and in the context of this inflammatory pathology, evidence of ongoing white matter degradation has also been observed (21). There is also evidence that increased microglial activation can be present up to 17 years after TBI (23). Moreover, TBI could be viewed as a condition with a persistent inflammatory state as elevated serum interleukin (IL)-1β, IL-6, IL-8, IL-10, and TNF-α levels over the first year post-injury have been detected (22).

The terms brain injury-induced immunodepression syndrome (BIIDS) and stroke-induced immunodepression syndrome (SIDS) refer to dysregulation occurring as a result of trauma, brain surgery, spinal cord injury (SCI), or SAH (23-25).

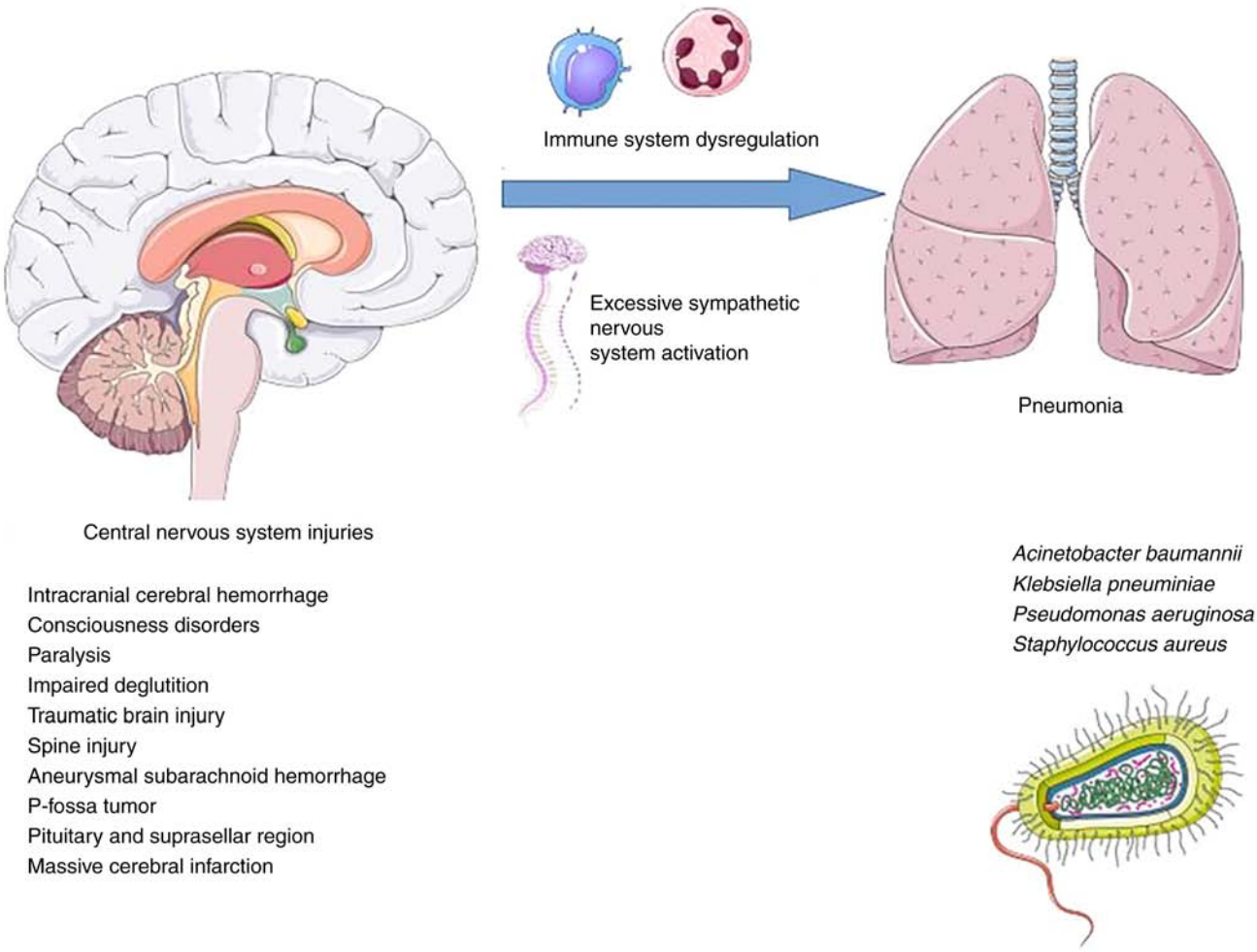

Figure 1. Mechanisms responsible for pneumonia development in central nervous system injuries. Parts of the figure were drawn by using images from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

SIDS is thought to have two phases. The early transitory activation of the first phase begins as soon as 12 h after the first injury and lasts for up to 24 h. The second phase is characterized by a systemic immunodepression that can last for many weeks (26-28).

Immunosuppression also develops from prolonged catecholamine release. Catecholamines are released after a brain injury because the hypothalamic-pituitary axis and sympathetic nervous system are engaged. Inflammatory response, as previously stated (29-31), can also be brought on by this. Additionally, the reaction is also mediated by 2-adrenergic receptors (32). In patients with brain injuries, infections are strongly correlated with increased sympathetic system activity, elevated catecholamine levels, and immunosuppression (33-35).

According to previous research (36), putamen and right frontal injuries render patients more vulnerable to infections. Due to their link to excessive sympathetic activation, which directly promotes cardiac and vascular alterations and leads to increased vigilance, heart rate, and blood flow to the skeletal muscles, insular brain strokes are associated with the highest risk of pneumonia (37).

The mechanisms responsible for pneumonia development in CNS injuries are illustrated in Fig. 1 and the mechanisms involved in immune system dysregulation caused by CNS injuries are illustrated in Fig. 2.

4. Prevalence of pneumonia due to MDR pathogens in CNS injuries

All the studies providing data regarding pneumonia due to MDR pathogens in CNS injuries are summarized in Table I (38-45). Regarding patients with TBI and pneumonia, the prevalence of MDR pneumonia ranges between 5.4 and 29.6%, according to different studies (39,40). In a study by Yang *et al* of the 324 patients with intracranial cerebral hemorrhage, 122 developed pneumonia, of whom 42 (34.2%) had MDR pathogen isolation (41). The reported incidence of MDR pneumonia among patients with various CNS injuries and pneumonia ranges between 8.5 and 42.2% (42,43). In a previous study including 89 patients with subarachnoid hemorrhage, intracerebral hemorrhage, and massive cerebral infarction, Teng *et al* found that among 40 patients who developed pneumonia, 15 (37.5%) had MDR pathogens (44).

In a study by Beghi *et al* which included 61 individuals with TBI, 8 patients developed pneumonia in a rehabilitation unit, of whom 6 (75%) had an MDR pathogen isolation (4).

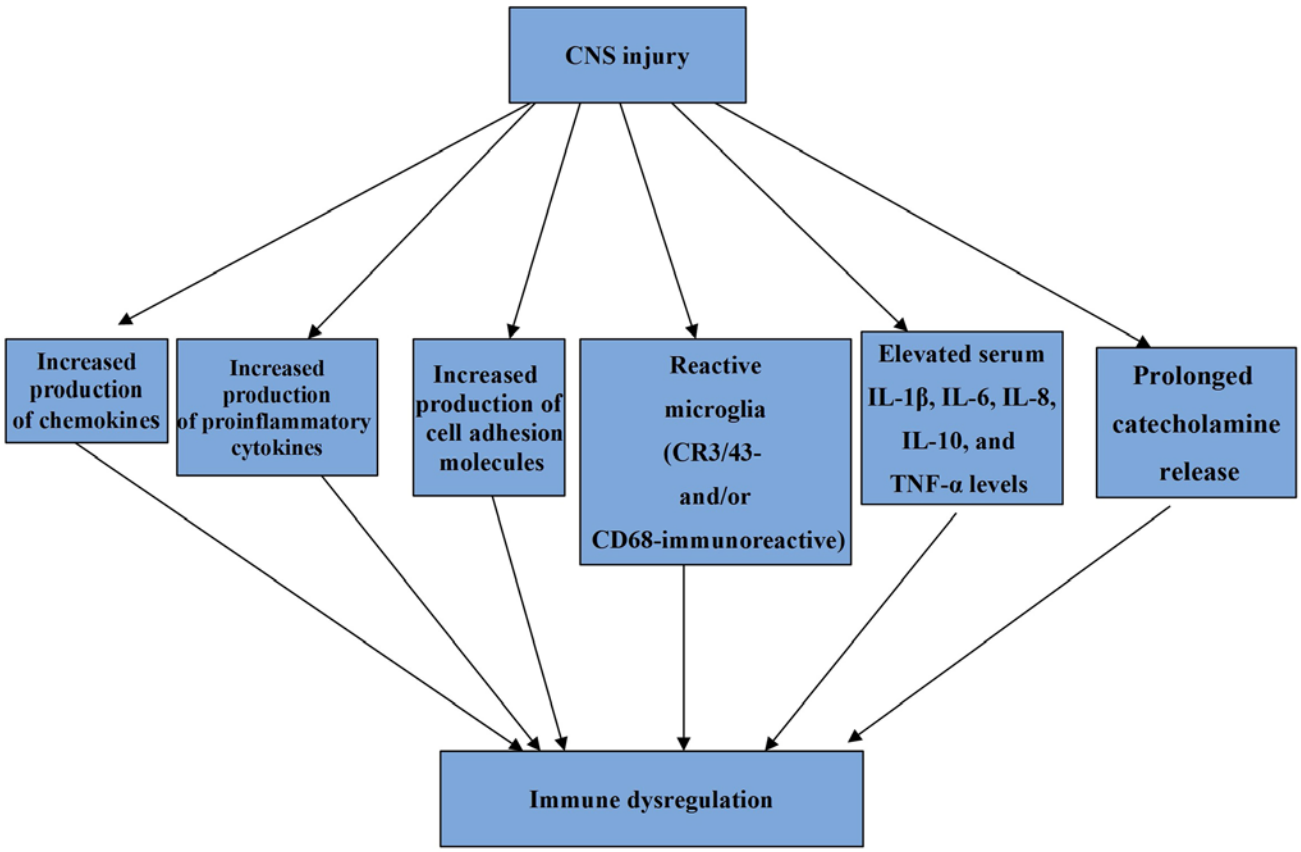

Figure 2. Mechanisms involved in immune system dysregulation caused by CNS injuries. CNS, central nervous system; IL, interleukin; TNF, tumor necrosis factor.

In addition, Jiang *et al* in a recent study of 575 patients with consciousness disorders, paralysis, and impaired deglutition who were admitted to a rehabilitation unit, recorded 427 episodes of pneumonia, of which 79 (18.5%) were MDR pneumonia (45).

5. Risk factors for pneumonia due to MDR pathogens in CNS injuries

Given the worsening patient outcomes and the significant expenses affecting the healthcare system as a result of greater lengths of stay and prolonged duration of treatment, it is critical to be able to identify which patients are at higher risk of developing pneumonia due to MDR pathogens.

Patients with TBI acquire nosocomial infections at a rate of 41%, with pneumonia being the most frequent, with a prevalence rate of ≥30% (45). Surgical procedures, prolonged hospitalization, CNS injury, CSF leak, administration of barbiturates, nasal carriage of S. aureus, and the necessity for intubation and mechanical ventilation have all been found to play a significant role in pneumonia development in these patients (46). Furthermore, patients with the following features had a higher risk of developing pneumonia: Intubation on the scene or in the emergency department; younger age; lower Glasgow Coma Scale (GCS) score; males; prolonged mechanical ventilation; higher injury severity score (ISS), and additional brain injuries (47). Table II summarizes identified risk factors for pneumonia due to MDR pathogens in CNS injuries as well as their prevalence in cases of pneumonia due to MDR pathogens among various studies (40,42-45).

6. Microbiological data

Common microorganisms involved in pneumonia due to MDR pathogens in CNS injuries are presented in Table I.

Rare causes of pneumonia in immunocompromised patients may include microorganisms which may rarely be encountered in immunocompetent patients (48). For example, cases of severe invasive infections such as pneumonia due to *C. striatum* may occur especially among immunocompromised patients who have a history of long hospital admissions, numerous courses of antibiotics, and/or those who have used invasive medical devices (49,50). According to some studies, *Corynebacterium spp.* should also be considered as potential pathogens, and suspicious isolates should be identified to the species level since *C. striatum* is frequently MDR (51,52).

Regarding Gram-positive MDR pathogens, of great interest is a study that examined the proportion of MDR of common bacteria isolated from hospitalized neurology patients with pneumonia in ICU and non-ICU settings, between the early and late years of the period 2007-2016. The prevalence of MDR among infections caused by *S. aureus* and *S. pneumoniae* did not differ significantly between the early and late study periods. *S. pneumoniae* exhibited sensitivity to penicillin, ceftriaxone and levofloxacin, especially during the late study period and resistance to tetracycline,

Table I. Studies describing patients with CNS injuries and pneumonia due to MDR pathogens.

Study	CNS injury	Participants	Pneumonia	Pneumonia due to MDR pathogens	MDR pathogens
Yang *et al*, 2022 (41)	Intracranial cerebral hemorrhage	324	122	42/122 (34.2%)	*A. baumannii* (40.5%) *K. pneumoniae* (26.2%) *P. aeruginosa* (23.8%)
Jiang *et al*, 2022 (45)	• Consciousness disorders • Paralysis • Impaired deglutition	575	427	79/427 (18.5%)	*A. baumannii* (45.3%) *P. aeruginosa* (36.8%) *K. pneumoniae* (12.6%) *E. cloacae* (1.1%) *S. aureus* (4.2%)
Lee *et al*, 2019 (42)	Various CNS illnesses	277	351	148/351 (42.2%)	*A. baumannii* (23.6%) *S. pneumoniae* (5.4%) *P. aeruginosa* (4%) *K. pneumoniae* (14.9%) *K. aerogenes* (1.4%) *S. aureus* (45.3%)
Shrestha *et al*, 2019 (43)	• Traumatic brain injury • Spine injury • Aneurysmal SAH • Miscellaneous • P-fossa tumor • Pituitary and suprasellar region	106	35	3/35 (8.5%)	*K. pneumoniae* (66.7%) *Acinetobacter spp*. (33.3%)
Beghi *et al*, 2018 (4)	Traumatic brain injury	61	8	6/8 (75%)	*P. aeruginosa* (33.3%) *K. pneumoniae* (16.6%) *P. mirabilis* (16.6%) *S. maltophilia* (16.6%) Methicillin-resistant coagulase-negative *Staphylococci* (16.6%)
Ye *et al*, 2022 (40)	Traumatic brain injury	230	230	68/230 (29.6%)	*A. baumannii* (45.2%) *K. pneumoniae* (23.3%) *P. aeruginosa* (16.4%) *S. aureus* (15.1%)
Leone *et al*, 2002 (39)	Traumatic brain injury	116	58	4/73 (5.4%)	*S. aureus* (100%)
Teng *et al*, 2022 (44)	• SAH • Intracerebral hemorrhage • Massive cerebral infarction	89	40	15/40 (37.5%)	*S. aureus* (20%) *B. cepacia* (20%) *K. pneumoniae* (20%) *C. striatum* (20%) *Acinetobacter spp* (20%)
Jovanovic *et al*, 2015 (38)	Traumatic brain injury	144	35	6/107 (5.6%)	*S. aureus* (100%)

CNS, central nervous system; MDR, multidrug-resistance; *A. baumannii*, *Acinetobacter baumannii*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *E. cloacae*, *Enterobacter cloacae*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *K. aerogenes*, *Klebsiella aerogenes*; *P. mirabilis*, *Proteus mirabilis*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *B. cepacia*, *Burkholderia cepacia*; *C. striatum*, *Corynebacterium striatum*; SAH, subarachnoid hemorrhage.

Table II. Identified risk factors for MDR pneumonia in CNS injuries.

Study	Type of CNS injury	Identified risk factors
Ye *et al*, 2022 (40)	Traumatic brain injury	Age >60 years (67.4%) Diabetes mellitus (45.7%) Chronic obstructive pulmonary disease (34.8%) Mechanical ventilation ≥7 days (69.6%) Transfer from other hospitals (17.4%)
Lee *et al*, 2019 (42)	Various CNS injuries	Risk factors for MDR i.e., antimicrobial agent use in the previous 90 days, hospitalization for 2 days in the previous 90 days, nursing home residency (61.6%)
Shrestha *et al*, 2019 (43)	Various CNS injuries	Head injury (45.7%) Spine injury (20%)
Teng *et al*, 2022 (44)	Subarachnoid hemorrhage Intracerebral hemorrhage Massive cerebral infarction	Age >65 years (57.5%) Therapeutic hypothermia (32.5%)
Jiang *et al*, 2022 (45)	Hospitalization in neurorehabilitation units	Recent antibiotic exposure (100%) Low albumin level (52.1%) Performance of tracheostomy (25%)

MDR, multidrug-resistance; CNS, central nervous system.

erythromycin and trimethoprim-sulfamethoxazole. *S. aureus* exhibited sensitivity to vancomycin, quinupristin/dalfopristin, chloramphenicol, rifampicin and teicoplanin and resistance to clindamycin, ciprofloxacin, moxifloxacin, tetracycline, erythromycin and trimethoprim-sulfamethoxazole during the early and the late study period (42). In a study by Shrestha *et al* including patients with various CNS injuries with MDR VAP, all Gram-positive pathogens were sensitive to co-trimoxazole (43).

In a study by Lee *et al* (42), both the ICU and non-ICU settings have experienced an increase in the proportion of cases with Gram-negative bacteria that are resistant to various antibiotics and in both settings, the percentage of non-susceptibility to amikacin and colistin remained low between the early and late years of the period 2007-2016 (42). In the study by Shrestha *et al* all Gram-negative bacterial strains were sensitive to colistin (43). Gram-negative organisms have recently been reported to be dominant in neurorehabilitation ward patients, with *Acinetobacter baumannii* (*A. baumannii*) being almost universally resistant to ciprofloxacin, imipenem, piperacillin, piperacillin/tazobactam and meropenem and *Klebsiella pneumoniae* (*K. pneumoniae*) being resistant to numerous antibiotics, except tigecycline, cefoperazone/sulbactam, sulfonamide, cefepime, and piperacillin/tazobactam (44).

7. Imaging data

Imaging data on patients with pneumonia due to MDR pathogens and CNS injuries is limited. A study investigating the pathogen distribution and imaging characteristics in patients with severe craniocerebral injuries with pneumonia due to MDR pathogens reported that the imaging features included consolidation, pleural effusion, and ground-glass opacities accounting for 63.24, 72.06 and 45.59%, respectively (40).

8. Prevention

In the neuro-ICU, proposed VAP prevention strategies include daily sedation interruption and a readiness-to-extubate evaluation; facilitation of early morbidity, elevating the head of the bed to 30-45˚; utilization of endotracheal tubes with subglottic secretion drainage ports and a closed/in-line endotracheal suctioning system; substituting the ventilator circuit if visibly soiled or malfunctioning; monitoring of residual gastric volume; early parenteral nutrition; and deep venous thrombosis prophylaxis (38). Other suggested preventive measures for VAP include antiseptic mouth wash, spontaneous breathing trial, and early extubation (15).

In addition, comprehensive rehabilitation approaches, including secretion management, training of respiratory muscles, airway clearance techniques, swallowing exercises, and pharyngeal electrical stimulation have been suggested for tracheotomized patients in neurorehabilitation units for the prevention of infections (47). Moreover, short-duration, high-dose antibiotic regimens appear to be effective in reducing the risk of antibiotic resistance (41).

An additional prevention approach is addressing brain injury-induced immunosuppression, which is mainly induced by sympathetic nervous system activation (53). With regard to microorganism infection in humans, the human host immunity response must be taken into account. Owing to the host immune defenses, most of the viral and bacterial infections are self-limiting to an immunocompetent host (54), and the microorganisms become commensal microorganisms if they can co-exist with human beings. In addition as indicated, MDR only becomes a significant issue when there is immunological dysregulation and immunosuppression in the host. Thus, eliminating immunological dysregulation and immunosuppression in patients with CNS injuries may provide a more feasible

therapeutic solution than targeting MDR microorganisms and eliminating these microorganisms.

The pivotal role of immunity in acquiring essential nutrition from the human microbiota (55-57) should also be considered. The human microbiome is essential to the health and wellbeing of individuals, as they are the indispensable source of metabolites for the body (57). In the case of acute infection, with the help of a special pathway of the innate immune defense, programmed cell death, such as apoptosis, necroptosis, and pyroptosis (58,59), both the microorganisms and damaged host cells will be destroyed and become a source of nutrition for healing.

By using these preventive strategies, the reduction of all pulmonary infections will result in the reduction of pneumonia caused by MDR bacteria.

9. Conclusions

The incidence of pneumonia due to MDR pathogens in CNS injuries varies among different settings, underlying injuries, and countries in which the studies were performed. Certain risk factors for the development of MDR pneumonia in ICUs and in neurorehabilitation units have been identified. The most frequently isolated microorganisms in pneumonia due to MDR pathogens in CNS injuries are *A. baumannii*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *S. aureus* with various patterns of resistance. The application of preventive strategies and the early detection and close monitoring of MDR strains may reduce the burden of antimicrobial resistance, which is now a global issue. Further multicenter prospective studies are needed to provide data on the clinical characteristics and outcomes of these patients as the data concerning these issues are limited.

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Authors' contributions

AG and VEG conceptualized the study. VEG, AAF, IT, GF, KF, KP and NT reviewed the data for inclusion in the review, and wrote and prepared the draft of the manuscript. VEG and GF provided critical revisions. Data authentication is not applicable. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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