Intensive Care Med _####################_
https://doi.org/10.1007/s00134-026-08606-z

NARRATIVE REVIEW

Ventilator-associated pneumonia after traumatic brain injury: a timing-sensitive ecological framework of neuroimmune–pulmonary vulnerability

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Abstract

Background: Ventilator-associated pneumonia (VAP) is frequent after traumatic brain injury (TBI), but its biological meaning and outcome impact remain incompletely defined. Traditional models emphasise mechanical ventilation, aspiration, colonisation, endotracheal tube biofilm, and hospital pathogens. These mechanisms remain essential, but they do not fully explain the early clustering, heterogeneous susceptibility, changing bacteriology, and variable mortality effect observed after TBI.

Main text: Severe brain injury creates an early vulnerable host state through impaired consciousness and airway protection, neuroimmune dysregulation, autonomic and endocrine activation, altered pulmonary immune surveillance, and, in many patients, extracranial trauma, shock, transfusion, or thoracic injury. These processes interact with ventilation, antibiotic pressure, and rapid respiratory microbiome disruption. Early VAP may reflect abrupt loss of control after injury and intubation, whereas late VAP may reflect persistent or secondary failure driven by biofilm maturation, antibiotic selection, multidrug-resistant pathogens, and intensive care unit (ICU)-acquired immune dysfunction. Clinically, VAP consistently prolongs ventilation, ICU stay, antibiotic exposure, and resource use, while its independent effect on mortality is phenotype- and context-dependent.

Conclusions: This model proposes a timing-sensitive ecological framework in which established mechanisms may converge early and with particular clinical intensity after severe TBI, creating a vulnerable host-microbe state that may lower the threshold for clinically apparent infection. Future studies should distinguish isolated TBI from polytrauma, compare TBI with other acute brain injuries and non-neurological ventilated populations, and incorporate dynamic immune, microbial, and trajectory-based outcomes.

Highlights

- VAP after TBI should be viewed as a timing-sensitive interaction between ventilator exposure and early host vulnerability, not as a distinct disease entity or as a pneumonia pathway unique to traumatic brain injury.
- The TBI-focused contribution lies in the early convergence of otherwise non-unique mechanisms: impaired airway control, aspiration risk, neuroimmune-endocrine activation, treatment exposure, dysbiosis, and extracranial injury burden, rather than in any single TBI-specific mechanism.
- Isolated TBI and TBI with polytrauma are biologically different phenotypes and should be separated in future studies.
- Early and late VAP may represent different phases of loss of pulmonary host–microbe containment; this distinction is probabilistic rather than TBI-specific in itself and requires validation in TBI-stratified cohorts.

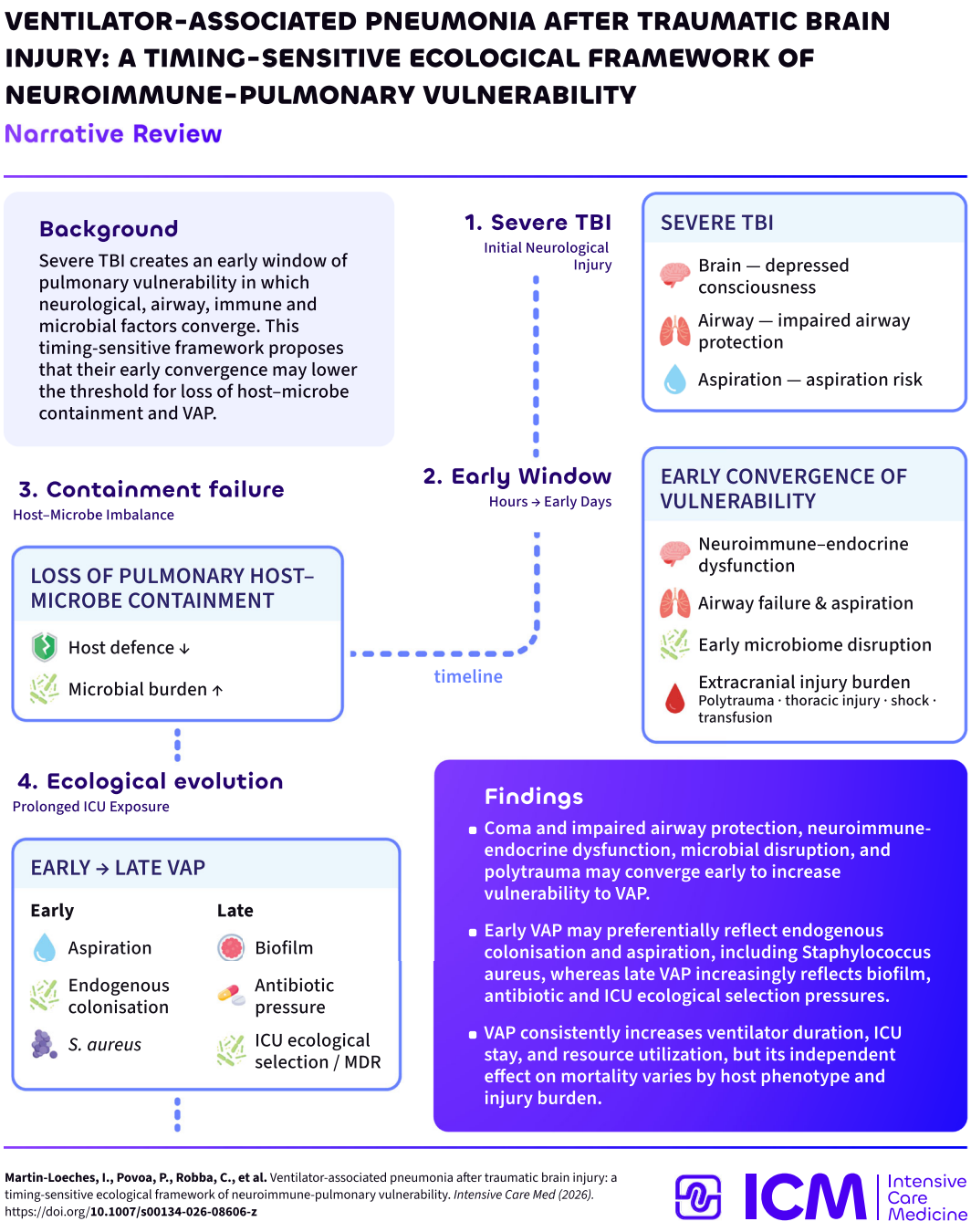
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• Mortality remains clinically relevant but context-dependent; VAP more consistently modifies recovery trajectory, ventilator dependence, ICU stay, antibiotic exposure, and possibly neurological recovery.

Keywords: aspiration, compartmentalised immunity, dysbiosis, neuroimmune-endocrine dysfunction, polytrauma, recovery trajectory, respiratory microbiome, traumatic brain injury, Ventilator-associated pneumonia, ventilator-associated tracheobronchitis

Graphical Abstract



Introduction

Ventilator-associated pneumonia (VAP) remains one of the most frequent infectious complications in mechanically ventilated patients. Its reported incidence varies widely because diagnostic criteria are imperfect and ventilator-associated lower respiratory tract infections form a biological spectrum rather than sharply separated syndromes [1–4]. In traumatic brain injury (TBI), this uncertainty is amplified by fever, neuroimmune-endocrine activation, sedative exposure, intracranial pressure-directed therapies, atelectasis, aspiration, and altered consciousness.

Patients with TBI have a high risk of VAP, with pooled estimates around one third of ventilated patients and higher rates in severe brain injury cohorts [5–7]. Exposure remains central; however, exposure alone does not explain why VAP often appears early, why only some exposed patients progress from colonisation to infection, why microbiology changes over time, or why mortality effects differ across cohorts despite consistent increases in ventilation duration and intensive care unit (ICU) stay.

The proposed model is temporal and integrative, not taxonomic: the aim is to clarify how established VAP mechanisms may be compressed into an early high-risk window after severe TBI, rather than to define a new VAP subtype.

The elements of this broader proposition are not individually new. Microaspiration, endotracheal tube biofilm, antibiotic pressure, brain-lung immune crosstalk, central nervous system injury-induced immune depression, ICU-acquired immune dysfunction, compartmentalised pulmonary inflammation, respiratory microbiome disruption, and host-pathogen imbalance have all been described in mechanically ventilated ICU populations [1, 2, 8, 9], including other acute brain injuries such as ischaemic stroke and subarachnoid haemorrhage [10–14].

This review therefore does not propose VAP after TBI as a distinct nosological entity. Rather, it uses TBI as a clinically relevant model in which established mechanisms may converge early and with particular clinical intensity. Figure 1 summarises this reframing.

What is specific to TBI?

VAP after TBI should not be framed as a separate disease entity.

What may be distinctive in TBI is the early convergence of vulnerability domains. Severe TBI combines abrupt neurological injury, depressed consciousness, impaired cough and swallowing, frequent emergency intubation, aspiration risk, sedative exposure, intracranial pressure-directed therapies, and mechanical ventilation initiated primarily for airway protection or cerebral physiological control rather than for primary lung infection [15–17]. These factors may lower the threshold at which colonisation or aspiration progresses to clinically apparent infection.

Cross-diagnostic comparisons also suggest a greater VAP burden after TBI. In a prospective multicentre cohort of mechanically ventilated patients, VAP occurred in 8% of patients with brain trauma, compared with 4% in both haemorrhagic and ischaemic stroke and 4% in non-neurological controls [18]. More recently, the ENIO international prospective cohort reported VAP incidence

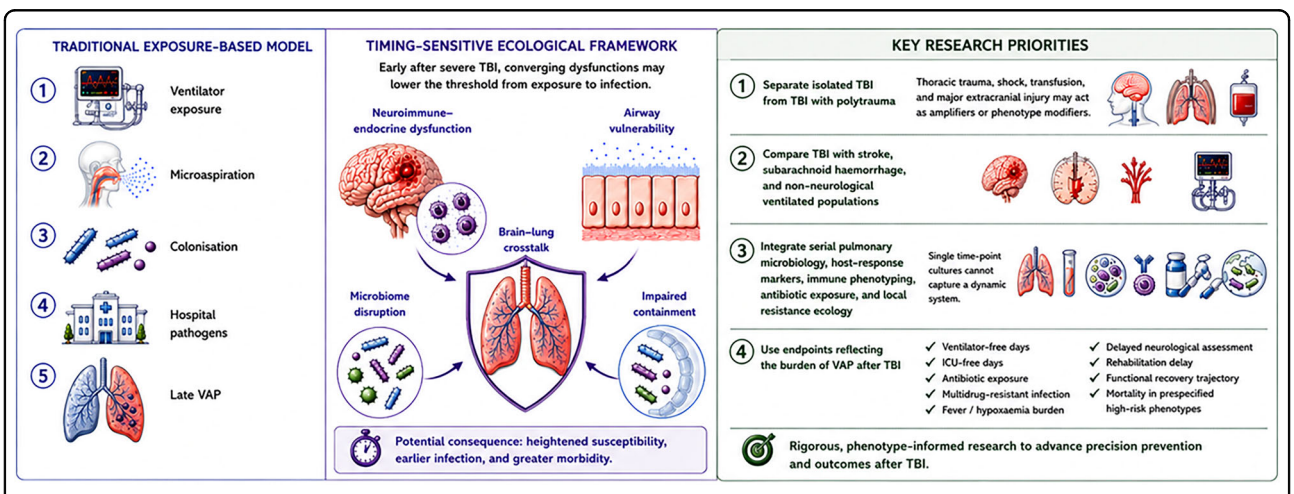


Fig. 1 Reframing ventilator-associated pneumonia after traumatic brain injury. The traditional exposure-based model is contrasted with a timing-sensitive ecological framework in which early neurological, airway, immune, and microbial vulnerabilities may converge after severe traumatic brain injury. The right panel summarises key priorities for future research. ICU, intensive care unit; TBI, traumatic brain injury; VAP, ventilator-associated pneumonia

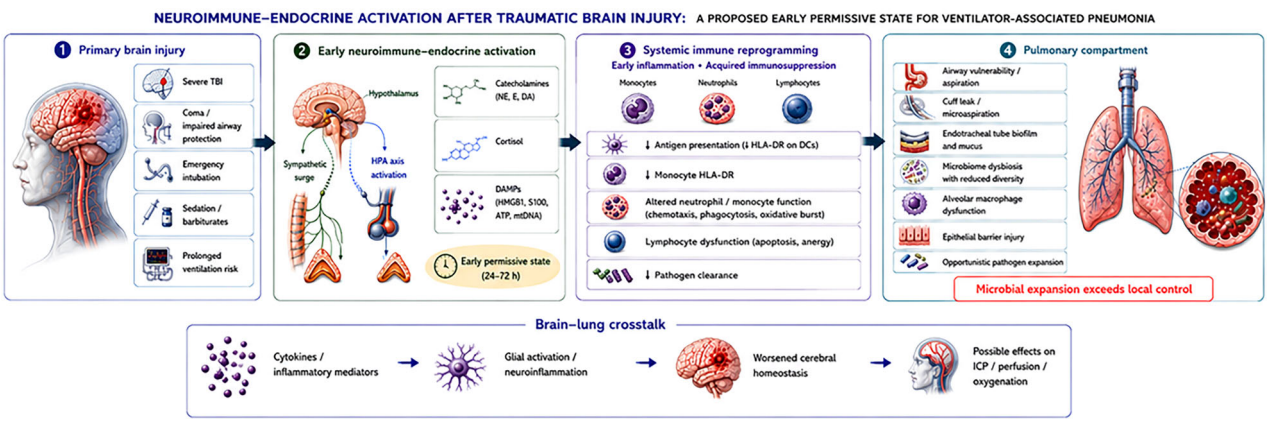


Fig. 2 Neuroimmune–endocrine activation after traumatic brain injury. Proposed sequence linking severe traumatic brain injury, early autonomic and endocrine activation, systemic immune reprogramming, pulmonary containment failure, and bidirectional brain–lung signalling. ATP, adenosine triphosphate; DA, dopamine; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; E, epinephrine; HLA-DR, human leucocyte antigen-DR; HMGB1, high-mobility group box 1; HPA, hypothalamic–pituitary–adrenal; ICP, intracranial pressure; mtDNA, mitochondrial DNA; NE, norepinephrine; TBI, traumatic brain injury; VAP, ventilator-associated pneumonia

densities of 16.6 episodes per 1000 ventilator-days in TBI, compared with 11.0 in intracerebral haemorrhage, 7.0 in aneurysmal subarachnoid haemorrhage, and 7.1 in ischaemic stroke [19]. However, these comparisons were not specifically designed to isolate the biological contribution of TBI from differences in injury severity, ventilation duration, and treatment intensity.

TBI may also contribute through neuroimmune-endocrine pathways. Acute central nervous system injury can be followed by systemic immune dysregulation, involving sympathetic and hypothalamic–pituitary–adrenal activation, damage-associated molecular patterns (DAMP) release, reduced antigen presentation, lower monocyte HLA-DR expression, altered monocyte and neutrophil function, lymphocyte dysfunction, and impaired pathogen clearance [10, 20–25]. These mechanisms are not exclusive to TBI, but in severe TBI they may occur early, in parallel with airway-control failure and invasive ventilation.

A further distinction is required between isolated TBI and TBI with extracranial injury. Thoracic trauma, haemorrhage, shock, transfusion, aspiration before intubation, and major extracranial injury are not neutral confounders; they may amplify systemic inflammation, immune suppression, transfusion-related immunomodulation, lung injury, gut barrier dysfunction, bacterial translocation, and exposure to invasive ICU procedures [26, 27].

Available trauma data suggest that chest trauma, especially when combined with TBI, increases the risk of post-traumatic pneumonia, and that both neurological and extracranial injury burden may influence VAP risk [28, 29].

In a prospective population-based cohort of patients with severe TBI, VAP occurred in 45% of patients. Patients with polytrauma showed a higher, although not statistically significant, VAP risk than those with isolated head injury (risk ratio [RR] 1.7, 95% confidence interval [CI] 0.9–3.1) [30]. Complementary trauma data showed post-traumatic pneumonia in 14.8% of patients with TBI without severe chest injury, 30.8% of those with combined TBI and severe chest injury, 26.8% of patients with severe chest injury without TBI, and 10.0% of those with neither TBI nor severe chest injury [28]. Isolated TBI and TBI with polytrauma should therefore not be analysed as biologically interchangeable phenotypes.

The most defensible TBI-focused hypothesis is not that TBI creates a unique pneumonia pathway, but that severe TBI aligns several vulnerability domains within a narrow early time window: neurological coma, airway-control failure, neuroimmune-endocrine activation, invasive ventilation, and variable extracranial injury burden.

Epidemiology and timing: why early clustering matters in TBI

The epidemiology of VAP after TBI is defined by timing as well as frequency. In CENTER-TBI, VAP occurred in approximately one in five patients and developed at a median of five days [5]. More granular data from a prospective cohort of 144 mechanically ventilated patients with severe TBI showed that early- and late-onset VAP, according to study-specific definitions, occurred in 24.3% and 26.4% of the overall cohort, respectively, whereas 49.3% remained VAP-free [29]. In the TAVeM study, ventilator-associated tracheobronchitis (VAT) and VAP frequently occurred during the first week of mechanical ventilation

[31]. Recent microbiome studies in patients intubated for non-pulmonary neurological conditions also show early microbial shifts and VAP clustering during the first days of ventilation [32]. This temporal pattern indicates that exposure acts on a host whose susceptibility is already being shaped within hours of injury and intubation.

Interventional data support this time-sensitive interpretation. In acute brain injury, early ceftriaxone prophylaxis reduced early VAP but did not affect late infections or mortality [33]. Meta-analytic data on antibiotic prophylaxis point in the same direction: early antimicrobial intervention can reduce early VAP but has not established a general mortality benefit and raises unresolved concerns about selection pressure [34]. These findings do not justify routine broad prophylaxis; they identify a short early window in which aspiration, airway vulnerability, immune dysfunction, and microbial instability converge.

The relevance of the early-late distinction in TBI lies in the timing of the neurological insult and in the abrupt transition in airway control, immune regulation, and pulmonary ecology after injury and intubation. Late VAP should not be reduced to cumulative exposure alone. Early and late VAP in TBI may therefore be viewed as probabilistic phases of host–microbe containment failure rather than as sharply separated entities.

Neuroimmune-endocrine triggering and brain-lung crosstalk

The link between TBI severity and VAP susceptibility is not only mechanical. More severe neurological injury increases coma, aspiration risk, need for intubation, sedative or barbiturate exposure, ventilation duration, and intensity of ICU interventions; in TBI cohorts and meta-analyses, neurological severity and treatment intensity, including high Abbreviated Injury Scale (AIS) head score, barbiturate infusion, tracheostomy, and prolonged mechanical ventilation, have been associated with VAP risk [5, 6, 35].

In this model, neuroimmune-endocrine dysfunction is not simply a background risk factor. It may act early, creating a permissive state in which airway failure, autonomic–endocrine activation, systemic immune reprogramming, and pulmonary immune dyscoordination converge before prolonged ventilator exposure has accumulated. This remains a biologically plausible hypothesis rather than a validated bedside mechanism, and should be tested against alternative explanations including injury severity, polytrauma, aspiration burden, and treatment exposure. These systemic changes become clinically relevant when they intersect with the pulmonary compartment [36]. The lung is not simply a passive recipient of circulating immune signals: local cytokine activity, alveolar macrophage function, neutrophil recruitment, epithelial integrity, mucus properties, and microbial ecology may diverge from systemic blood measurements [2, 37]. VAP may therefore emerge when microbial expansion exceeds local control, not merely when bacteria are aspirated.

Conversely, pulmonary inflammation and infection can worsen neurological injury [38]. Cytokines and inflammatory mediators released during acute lung injury or pneumonia may reach the central nervous system, activate glial cells, promote neuroinflammation, and contribute to neuronal damage [39, 40]. Mechanical ventilation, especially when associated with high airway pressures or ventilator-induced lung injury, may further influence cerebral perfusion, intracranial pressure, and neuroinflammatory pathways [40].

The relationship between injury severity and containment failure is unlikely to be linear. Severity increases risk, but phenotype matters. A deeply comatose patient with isolated TBI, minimal extracranial injury, and short ventilation differs from a patient with severe TBI, chest trauma, shock, massive transfusion, prolonged sedation, and early broad-spectrum antibiotics. Figure 2 summarises these interactions.

The pulmonary ecological sequence

Aspiration remains central, but its clinical consequence depends on the host and pulmonary ecological context. Microaspiration is common in mechanically ventilated patients because of impaired airway protection, secretions above the cuff, endotracheal tube leakage, and biofilm formation [1, 2, 9]. Regular cuff-pressure measurement and monitoring are therefore essential to limit underinflation-related leakage while avoiding excessive pressure on the tracheal mucosa. Yet many patients aspirate or become colonised without developing VAP. The decisive step is therefore not exposure to bacteria alone, but the loss of local containment once bacterial growth exceeds host control.

The respiratory tract should be viewed as a dynamic ecological system. During mechanical ventilation, microbial diversity may decrease, bacterial burden may rise, and opportunistic pathogens may expand [8, 32, 41]. These changes can occur rapidly and may precede clinical infection. In neurological injury cohorts, reduced microbial richness, enrichment of potentially pathogenic taxa, and cytokine-microbiota interaction patterns have been associated with subsequent VAP [36].

In the longitudinal PULMIVAP cohort of patients intubated for predominantly neurological, non-pulmonary indications, paired upper- and lower-airway sampling showed substantial microbial changes during mechanical ventilation. Patients who subsequently developed VAP showed a trend towards lower baseline microbial richness, together with enrichment of

potentially pathogenic taxa such as Escherichia-Shigella and Peptoniphilus, whereas Corynebacterium was more abundant in patients who remained VAP-free. Exploratory analyses also identified associations between airway taxa, local inflammatory mediators, and respiratory dysfunction, supporting an early and dynamic interaction between microbial ecology and pulmonary host response rather than a simple sequence of aspiration followed by infection [41].

These findings are not TBI-specific in isolation; their relevance lies in occurring within a host whose airway protection, autonomic regulation, and immune responses have already been altered by acute neurological injury.

Changing bacteriology over time fits this sequence. Early VAP after TBI may be enriched for organisms reflecting neurological injury, impaired airway protection, oropharyngeal aspiration, early colonisation, and abrupt immune-microbial disequilibrium, including *Staphylococcus aureus* in some cohorts [6, 36, 42].

In CENTER-TBI, *Staphylococcus aureus* was the leading isolate, detected in 80 of 196 VAP cases (40.8%), followed by *Haemophilus influenzae* (24.0%) and *Streptococcus pneumoniae* (8.2%) [5]. *Staphylococcus aureus* accounted for 161 of 350 VAP cases (46.0%) in a multicentre cohort of patients with severe brain injury [43]. In a prospective study of 100 intubated patients with head trauma, 68% were already tracheally colonised within 24 hours of intubation. Early-onset pneumonia developed in 26% of patients, and Staphylococcus aureus accounted for 44% of the causative isolates. In another prospective cohort of 109 patients with severe head trauma, admission nasal carriage of Staphylococcus aureus (odds ratio [OR] 5.1, 95% CI 1.9–14.0), aspiration before intubation (OR 5.5, 95% CI 1.9–16.4), and barbiturate use (OR 3.9, 95% CI 1.2–12.8) were independently associated with early-onset pneumonia [44, 45]. These findings support an endogenous colonisation–aspiration pathway in which severe coma, loss of cough and swallowing, aspiration during injury or emergency airway management, and impaired mucociliary clearance permit rapid transfer of pre-existing nasal or oropharyngeal flora into the lower respiratory tract, before antibiotic exposure and ICU selection pressures reshape the respiratory microbiota. However, direct comparative evidence establishing that the predominance of *Staphylococcus aureus* is greater in TBI than in other populations with early VAP remains limited.

Late VAP is more likely to reflect ICU ecological pressure: persistent containment failure, biofilm maturation, prolonged sedation, antibiotic selection, loss of microbial diversity, repeated procedures, ICU-acquired immune dysfunction, and selection of hospital-adapted or multidrug-resistant Gram-negative organisms, including *Pseudomonas aeruginosa* and *Enterobacterales* [46–48]. The selective effect of early antibiotic prophylaxis therefore supports a timing-sensitive model rather than a simple early-host versus late-exposure dichotomy. This distinction is probabilistic, but it supports the view that early and late VAP are different ecological states:

Colonisation, VAT, and VAP remain clinically useful labels, but biologically they may represent points along a continuum [4, 31, 46, 48]. Transitions between these states depend on bacterial burden, pathogen virulence, local immune response, epithelial injury, and ecological stability.

Clinical impact: morbidity, mortality, and recovery trajectory

VAP after TBI is consistently associated with morbidity. Patients who develop VAP generally require longer mechanical ventilation, longer ICU and hospital stay, more antibiotics, and greater resource use [5–7, 49]. In neurocritical care, prolonged sedation, fever, hypoxaemia, systemic inflammation, neuroimmune–endocrine activation, and ventilator dependence may also interfere with neurological assessment, rehabilitation, and recovery.

The association with mortality is more heterogeneous. Some cohorts, including recent single-centre data with substantial pathogen burden, report a significant mortality association [47]. Other adjusted analyses, including CENTER-TBI, found no independent association with mortality or six-month neurological outcome after accounting for confounders [5]. Meta-analyses also suggest that crude mortality associations may attenuate after adjustment for baseline severity, extracranial injury, and competing risks [6, 7]. This should not be interpreted as evidence that VAP lacks lethality. Rather, its mortality effect is likely phenotype-dependent and may become most apparent with high pathogen burden, late infection, severe extracranial injury, shock, multidrug-resistant pathogens, inadequate source control, profound immune dysfunction, or severe pulmonary involvement.

Mortality alone is therefore too crude an endpoint to capture the full burden of VAP after TBI. VAP can prolong ventilator exposure, increase antibiotic burden, worsen oxygenation, raise metabolic demand, trigger fever and systemic inflammation, and delay neurological assessment or rehabilitation. Even when it does not independently determine survival, it may alter the pace, complexity, and quality of recovery after TBI.

Prevention and monitoring: from exposure reduction to ecological stabilisation

Current VAP prevention remains essential. Head-of-bed elevation, oral care, subglottic secretion drainage, sedation minimisation, early mobilisation, when possible, cuff pressure control, and ventilator liberation reduce exposure and may reduce infection risk [50–53]. The ecological model does not

replace these measures; it argues that they may be complemented, in research settings and selected high-risk patients, by early identification of vulnerable host–microbe states.

Microaspiration illustrates this limitation. Subglottic secretion drainage reduces VAP incidence, but mortality effects are inconsistent [52, 53]. Reducing inoculum matters, but infection also depends on local host control. Similarly, early antimicrobial prophylaxis can reduce early VAP in selected acute brain injury populations, but must be balanced against antimicrobial selection pressure, local baseline risk, and the possibility of shifting rather than resolving ecological instability [33, 34, 54, 55]. Selective digestive tract decontamination also manipulates host-microbe ecology; post hoc data in acute brain injury suggest potential benefit, but broader ICU trial results and resistance concerns argue against simplistic extrapolation [56–58].

At present, early risk phenotyping should be viewed as a tool for surveillance, trial enrichment, and clinical vigilance rather than as a trigger for a specific biological treatment. No immune- or microbiome-directed intervention can currently be recommended specifically for TBI-associated VAP outside research settings. In the first 24–72 hours, clinicians and investigators may identify patients with converging vulnerability signals: severe coma, impaired airway protection, aspiration before or during intubation, high secretion burden, thoracic trauma, shock, transfusion, prolonged or deep sedation, early broad-spectrum antibiotics, worsening oxygenation, and microbiological evidence of loss of colonisation resistance. These are not diagnostic criteria for VAP. They are markers of a vulnerable host–microbe state in which established preventive measures, diagnostic vigilance, antimicrobial stewardship, and enrolment in targeted studies may be particularly relevant. Their clinical role is therefore to refine suspicion and research stratification, not to justify pre-emptive escalation of antimicrobial or biological therapy.

Until prospective data are available, microbiome-guided and immune-guided prevention should be considered investigational. Current care should remain centred on established VAP-prevention measures, timely diagnosis, source control when infection is established, and antimicrobial stewardship.

Research agenda

This framework is hypothesis-generating, not a validated bedside diagnostic tool and not a proposed disease classification. Its value will depend on whether it improves prediction, prevention, and outcome selection.

Future prevention trials should be phenotype-enriched and timing-sensitive as shown in Fig. 1. Rather than testing a single intervention in all ventilated TBI patients, studies should identify early biological states and match interventions to mechanisms, while explicitly separating isolated TBI, TBI with thoracic trauma, and TBI within broader polytrauma phenotypes. Four priorities follow. First, future cohorts should separate isolated TBI from TBI with polytrauma, thoracic trauma, shock, transfusion, and major extracranial injury. Second, TBI should be compared with stroke, intracerebral haemorrhage, subarachnoid haemorrhage, and non-neurological ventilated populations. Third, studies should integrate serial pulmonary microbiology, host-response markers, immune phenotyping, antibiotic exposure, and local resistance ecology, because single time-point cultures cannot capture a dynamic process. Fourth, trials should use endpoints that reflect the burden of VAP after TBI: ventilator-free days, ICU-free days, antibiotic exposure, multidrug-resistant emergence, fever and hypoxaemia burden, interruptions to neurological assessment, rehabilitation delay, functional recovery trajectory, and mortality in prespecified high-risk phenotypes.

Conclusion

VAP after TBI should not be viewed only as a late complication of ventilator exposure. It is better interpreted as infection emerging when ventilator exposure, aspiration risk, microbial disruption, and impaired pulmonary containment act on an early vulnerable neuroimmune-pulmonary host state. This does not make all mechanisms TBI-specific: aspiration, biofilm, dysbiosis, antibiotic pressure, and compartmentalised pulmonary immunity occur across ventilated ICU populations. What distinguishes TBI is their early convergence with neurological injury, impaired airway protection, neuroimmune-endocrine dysregulation, treatment exposure, and, frequently, extracranial trauma.

Early VAP may reflect immediate loss of host-microbe equilibrium after injury and intubation; late VAP may reflect persistence or secondary evolution of the same failure under biofilm, antibiotics, multidrug-resistant selection, and prolonged critical illness. This distinction remains probabilistic and should be tested in cohorts that separate isolated TBI, polytrauma, other acute brain injuries, and non-neurological ventilated ICU populations. This model explains why VAP consistently increases morbidity and resource use, while its independent mortality effect varies across cohorts and phenotypes.

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Authors' contributions

GC conceived the manuscript. All authors contributed to the intellectual content, critically reviewed and edited the manuscript, and approved the final version. GC and AG contributed to figure development and visualisation, with input and approval from all authors. GC supervised the work.

Funding

Open access funding provided by Università degli Studi di Milano - Bicocca within the CRUI-CARE Agreement.

Declarations

Conflict of interest

CR is a Deputy Editor of Intensive Care Medicine. She has not taken part in the review or selection process of this article. PP is a Senior Associate Editor for Intensive Care Medicine. He has not taken part in the review or selection process of this article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Use of artificial intelligence tools

Artificial intelligence-assisted tools, including ChatGPT, were used solely to support graphical development, visual refinement, and language editing. These tools were not used to generate scientific interpretation, select references, draw conclusions, or replace author judgement. All scientific content, figure content, and final text were critically reviewed, edited, and approved by the authors, who take full responsibility for the accuracy and integrity of the work.

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Received: 30 April 2026 Accepted: 20 August 2026
Published online: 29 October 2026

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