When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit

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Narrative Review

When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit

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Abstract

Background: Most Intensive Care Unit (ICU) patients receive broad-spectrum antibiotics. While lifesaving in some, in others these treatments may be unnecessary and place patients at risk of antibiotic-associated harms.

Objectives: To review the literature exploring how we diagnose infection in patients in the ICU and address the safety and utility of a “watchful waiting” approach to antibiotic initiation with selected patients in the ICU.

Sources: A semi-structured search of PubMed and Cochrane Library databases for articles published in English during the past 15 years was conducted.

Content: Distinguishing infection from non-infectious mimics in ICU patients is uniquely challenging. At present, we do not have access to a rapid point-of-care test that reliably differentiates between individuals who need antibiotics and those who do not. A small number of studies have attempted to compare early aggressive versus conservative antimicrobial strategies in the ICU. However, this body of literature is small and not robust enough to guide practice.

Implications: This issue will not likely be resolved until there are diagnostic tests that rapidly and reliably identify the presence or absence of infection in the ICU population. In the meantime, prospective trials that identify clinical situations wherein it is safe to delay or withhold antibiotic initiation in the ICU until the presence of an infection is proven are warranted.
Introduction

Prescribing broad-spectrum empiric antibiotics ‘just in case’ is the norm in the Intensive Care Unit (ICU)(1). An international point-prevalence study has demonstrated that, on a given day, 70 percent of all patients in ICUs are administered at least one antibiotic(2). While on one hand antibiotics are lifesaving therapies in infected patients, they do not benefit non-infected patients and place them at risk for potential antibiotic associated adverse events.

Antibiotic-associated harms include adverse drug events (ADEs), risk of secondary opportunistic infections, and antimicrobial resistance (AMR)(3-6). Antibiotic-associated ADEs are common in ICU patients, due partly to the underlying critical illness that increases susceptibility to organ injury(4), as well as the multiplicity of medications that ICU patients receive that increase the risk of undesirable drug interactions(5).

The individual and collective ecological harms of antibiotics are well documented in the ICU(7). Certain classes of antibiotics commonly used in the ICU have a propensity to cause ecological “collateral damage” via a loss of microbial diversity and selection for organisms such as Clostridioides difficile and Candida spp. that can cause secondary infection (8-13). Further, a significant increase in the carriage of resistant bacteria has been demonstrated to occur with even brief antibiotic exposure (1-3 days) in ICU patients (14).

Antibiotic de-escalation has been proposed as a potential compromise to address the competing goals of rapid and effective treatment of potential infection and reducing antibiotic overuse and resultant unnecessary antibiotic harms(15). However, strong evidence demonstrating that antibiotic de-escalation is a reliable strategy in patients in the ICU is
lacking, partly due to a lack of a clear definition of what de-escalation involves. Antibiotic
de-escalation strategies have not yet been shown to be effective in reducing the carriage of
MDR bacteria and it may increase the incidence of secondary infections(16, 17).

We therefore propose that the ideal approach, if proven safe, would be to avoid initiation of
antibiotics in the ICU patient until the treating clinician were convinced of the presence of
infection and its source. The following narrative review aims to explore the literature that
addresses how we diagnose infection in the ICU and whether clinicians working with ICU
patients can confidently employ a “watchful waiting” strategy, with the resultant benefit of
avoiding unnecessary antibiotic exposure and thus harms.

There have been previous reviews that have addressed how to reduce antibiotic exposure in
ICU patients(18-21). Our narrative review attempts to specifically focus on the question of
how to avoid the initiation of antibiotics in the high stakes environment of the ICU.

Methods

A literature search using the PubMed and Cochrane Library databases for published English
language articles within the past 15 years was conducted by one of the authors (KJD).
Relevant additional articles identified ad hoc by all authors were also included.

The following types of articles were included: randomised controlled trials, meta-analyses,
observational (small and large), expert opinions, and guidelines. Search terms included were
‘intensive care’ AND ‘(antibiotics OR antimicrobials)’ AND (overuse OR empiric OR
delayed OR conservative OR timing OR culture negative OR biomarkers OR unnecessary
OR inappropriate). The initial search strategy identified 2747 results obtained, those deemed to be relevant to this narrative review on when not to start antibiotics in the ICU were included.

**Does This Patient in the ICU Have an Infection?**

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated response to infection(22). However, whilst identifying organ dysfunction is relatively straight-forward, prospectively diagnosing infection as the cause of organ dysfunction is more challenging. The difficulty in the bedside diagnosis of sepsis was highlighted by a cohort study in the Netherlands, where of 2579 patients who presented to the ICU with clinically suspected sepsis, 13% had a post hoc infection likelihood of “none” and an additional 30% of “possible”(23).

Diagnosing infectious complications in existing ICU patients is fraught with problems. Clinical signs (e.g. pyrexia, tachycardia, vasoplegia) and laboratory findings (e.g. leucocytosis/leucopenia, hyperlactatemia) that are often attributed to infection are commonly associated with non-infectious aetiologies in the ICU population(24-28). Even clinical signs that may suggest a specific source of infection (e.g. lung consolidation, increased sputum production) may be non-specific in ventilated ICU patients(29).

Microbiological cultures are the current ‘gold standard’ of confirming infection and a positive culture, ideally with input from a clinical microbiologist, facilitates the administration of appropriate antibiotics. However, current bacterial and fungal culture
techniques take time (typically > 24 hours), necessitate good (and sometimes invasive)
sampling techniques, and there is the potential for patient deterioration whilst awaiting
results. Even once culture results are obtained, the retrospective diagnosis of sepsis can be
problematic due to contamination, colonization, and “culture negative” infection. In patients
admitted to the ICU, 28-49% of patients with a syndrome consistent with likely sepsis have
negative cultures(30-34). Failure to identify an organism may be due to the patient receiving
prior antibiotics, thus obscuring conventional cultures, poor collection technique, or the
presence of unusual or slow-growing organisms(35, 36). Alternatively, the patient may have
a non-infectious cause for their clinical syndrome. For these reasons, even the retrospective
diagnosis of infection is problematic, as demonstrated in a study by Rhee and colleagues(37)
in which poor inter-rater reliability (Fleiss' $\kappa$ 0.21) was exhibited by critical care clinicians
when asked to in diagnose sepsis using a series of case vignettes.

There has thus been an increasing interest in exploring novel diagnostics that can quickly and
accurately differentiate between those patients with and without infection. Diagnostics can be
broadly differentiated into two groups: (1) diagnostics that identify the presence of microbes,
and (2) biomarkers that identify the host response to the presence of microbes. Assays that
aim to identify the presence of microbes faster than conventional microbiological cultures are
in various stages of development(38-40). However, these assays remain susceptible to the
problems of contamination and colonization, leading to the identification of microorganisms
that are not necessarily responsible patient deterioration - problems which may or may not be
solved with emerging next generation sequencing diagnostic technology(41).

Host biomarkers have shown varying levels of promise in guiding antibiotics in the ICU
environment(42-44). Procalcitonin has been shown to be helpful in reducing the duration of
antibiotic therapy, albeit this reduction is often modest(45). Other proposed biomarkers of
sepsis include c-reactive protein(46, 47), various cytokines(48, 49), adhesion molecules(50),
hormones(51), receptors(52-55), and surface glycoproteins(56). There is also increasing
interest in the role of “omic” technologies (genomics, metabolomics, transcriptomic,
proteomic) in the diagnosis of sepsis(57). However, the utility of currently available host
biomarkers in distinguishing between ICU patients with and without infection, and thus
guiding antibiotic initiation, remains low(7, 44, 58-63).

It is hypothesized that, given the biological complexity of sepsis, a stratification strategy
based on a panel of multiple biomarkers such as gene expression has more potential to meet
the needs of an ideal biomarker-based stratification tool(27, 64, 65). Such biomarker tests
remain in their infancy and we await prospective studies to determine their utility in clinical
practice.

Can We Afford to “Watch-and-Wait” for Infection in an ICU Patient?

Whilst we wait for improved diagnostic tools that allow us to more quickly and accurately
identify the presence of infection in patients in the ICU, is it safe to adopt a more
conservative approach to antimicrobial prescribing? Is it safe for the treating clinicians to
delay empiric broad-spectrum antibiotics in an ICU patient until the likely source of infection
or another non-infective diagnosis becomes apparent?

The Surviving Sepsis Campaign (SSC) guidelines recommend that antibiotics be initiated
within one hour from recognition of sepsis(66). However, data investigating this
recommendation have been inconsistent, particularly in patients without shock, and suffer from the biases inherent in time-to-intervention trial design (e.g. treatment delay in more complicated patients) (67-72). Further, many studies in this area lack critical information regarding how infections were confirmed, whether antibiotic selection was appropriate, and/or when (or whether) source control was achieved.

Initial inappropriate antibiotic therapy has been demonstrated to be an independent risk factor for mortality in ICU populations (73-75), where inappropriate was defined retrospectively as empiric antibiotics that were unlikely to treat the causative pathogen. Source control is also vital to preventing increased mortality (76, 77). In a large prospective observational study by Bloos and colleagues (76), there was no mortality benefit from the early initiation of antimicrobial therapy – defined as antibiotic administration that occurs within the first hour of the onset of infection-related organ dysfunction. However, inadequate source control was shown to increase 28-day mortality from 26.7 to 42.9%. We therefore hypothesise that the importance of timeliness with regards to antibiotic administration may be overemphasised, and rather a more nuanced approach wherein brief delays in antibiotic administration to allow for source recognition, source control, and ensuring antibiotic appropriateness may be valid.

Further, it is unclear as to whether we should distinguish between patients who are admitted to the ICU with likely infection and those with a critical illness who develop an infection as a secondary complication. Sepsis is not a homogenous syndrome, with a phenotype that varies based on both characteristics of the culprit organism and characteristics of the host immune response (78).
ICU-acquired infections are associated with different microbiological isolates than those acquired in the community, and are often associated with resistant organisms(2, 79). This may be, in part, due to different environmental risk factors (e.g. central vascular catheters, endotracheal tubes), previous exposure to antibiotics (e.g. antimicrobial prophylaxis for surgery), and an altered microbiome characterised by a loss of microbial richness and diversity(80, 81). The presence of critical illness also results in an altered immunophenotype, characterised by the concurrent upregulation of multiple pro- and anti-inflammatory pathways, with downregulation of adaptive immune pathways(82). Of note, the immunophenotype of critical illness, and associated risk of secondary nosocomial infection, is remarkably similar independent of whether the initial insult had an infectious or non-infectious aetiology(82, 83).

On the other hand, ICU patients may also have protective factors – namely, close monitoring of physiology and one-to-one nursing – that may mean that “watchful waiting” in the ICU is a safer strategy compared to other populations. Hranjec and colleagues(84) attempted to address the safety of delayed initiation of antimicrobial therapy in a cohort of surgical ICU patients by performing a quasi-experimental, before-and-after observational cohort study that compared an aggressive treatment strategy (early antibiotic treatment for suspected infection) to a conservative one (antimicrobial treatment only after objective findings confirmed infection). They concluded that waiting for objective data to diagnose infection prior to antimicrobial treatment was not associated with increased mortality. However, antibiotic appropriateness was low, with only 62-74% of patients receiving appropriate antibiotic regimens, and the case-fatality rate high. Further, patients received prolonged courses of antibiotics (12-17 days), which itself is associated with adverse outcomes(85, 86).
In another study, Amaral and Holder (87) investigated whether delays in antimicrobial therapy increased mortality in a specific condition in the ICU, ventilator associated pneumonia (VAP). In this single-centre retrospective study, there was no association between timing of antibiotics after the identification of a ventilator-associated complication and patient harm (mortality, super-infection, or treatment failure) in patients subsequently diagnosed with VAP.

However, the above single-centre studies can only be, at best, hypothesis-generating given their significant and numerous limitations. Future studies are thus required to determine whether delayed prescribing strategies for selected patients in the ICU setting is safe, feasible and beneficial. In the meantime, we have provided some recommendations for daily practice of antibiotic initiation in the ICU based on expert interpretation of available evidence (Table 1).

What Future Research Do We Need?

The above narrative review of the literature highlights two key gaps in the evidence that need to be addressed so that clinicians can safely and confidently avoid unnecessary antibiotic initiation in the ICU. Firstly, we need novel diagnostic strategies to help us better identify the presence of infection and, secondly, we need high quality multi-centre prospective randomised studies to inform us when ‘watchful waiting’ may be a safe and effective approach in the ICU. Potential future approaches to address these gaps in the literature will be discussed in turn.
Improving our ability to identify infection, and distinguish it from non-infectious mimics, is the ultimate solution to reducing unnecessary antibiotic initiation in the ICU. We propose that an ideal diagnostic tool for infection would quickly, accurately, and affordably identify the presence or absence of a specific pathogen, any antibiotic resistance genes, and a host response to a pathogen(78). Identifying the host response to infection is necessary to differentiate between colonisation or contamination with true infection. An ideal tool would also be able to monitor the response to treatment, and facilitate the cessation of antibiotic treatment(61). It is essential that any proposed diagnostic tests are evaluated against clinically important outcome measures (e.g. mortality, morbidity).

However, until such a diagnostic tool becomes available that has the sensitivity and specificity to safely distinguish those critically ill patients who need antibiotics from those who do not, we recommend that additional studies are required that aim to determine whether a ‘watchful waiting’ approach to antibiotic prescribing is both safe and beneficial to selected ICU patients.

Clinical researchers additionally need to consider what are the most practical ICU subgroups in which to trial this approach. We recommend that studies investigating the safety of delayed prescribing: (i) focus on specific sub groups of patients (e.g. trauma, burns, or patients with febrile neutropenia); (ii) exclude patients who are hypotensive due to suspected infection(30); and, (iii) initially focus on patients who are already in the closely monitored environment of the ICU who may have developed an infectious complication (versus an initial presenting complaint of possible infection). The latter is recommended as the harms of delayed prescribing in certain populations (e.g. suspected meningococcal meningitis) is likely to be significantly greater than that of others (e.g. VAP). Whilst we await further evidence
regarding antibiotic initiation in patients in the ICU, we have summarised a suggested
approach to the question “Do I Need to Give Antibiotics?” in Figure 1.

Future studies also need to measure and adjust for other important contributors to treatment
failure, including: the appropriateness of empiric antibiotic selection(73-75); the
appropriateness of antibiotic dosing based on the unique pharmacokinetic and
pharmacodynamic changes seen in ICU patients(7, 88); and the timeliness and thoroughness
of source control(76, 77). We hypothesise that, for some subgroups of ICU patients, the
benefit of early empiric antimicrobial treatment (versus delayed targeted antimicrobial
treatment) is likely to be minimal if appropriate antibiotic selection, adequate dosing, and
efficient source control is achieved. We have outlined future research strategies and
directions in Table 2.

Conclusions

In the future, we will inevitably have the luxury of a rapid testing and management tool
whereby only ICU patients who have an infection will receive antibiotics. However, at
present we must continue to integrate the available clinical, laboratory, and radiologic
information in order to optimize management with nearly all patients with infections
receiving antibiotics while minimizing these treatments in non-infected patients. This
approach relies heavily on shared decision-making between intensivists and experts in
infectious disease and clinical microbiology. The definitive answer to the problem of
antibiotic overuse in the ICU is the development of point-of-care diagnostic technologies that
will allow for the quick and reliable diagnosis of infection. In the meantime, trials that
identify when or if it is safe to delay antibiotic initiation in the ICU until an infection is proven are needed before this approach can be widely implemented.

Tables and Figures

**Recommendations for Daily Practice**

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source control in a critically ill patient with sepsis should not be delayed.</td>
</tr>
<tr>
<td>In the non-shocked ICU patient with suspected infection (and onset &gt; 48 hours after ICU admission) consider delaying the initiation of antimicrobial therapy until after initial investigations aimed at sepsis diagnosis and source identification.</td>
</tr>
<tr>
<td>In patients with proven infections, do not unnecessarily defer antibiotics.</td>
</tr>
<tr>
<td>Currently available host biomarkers such as C-reactive protein (CRP) and Procalcitonin (PCT) have no place in routinely guiding the initiation of antibiotics in the ICU.</td>
</tr>
</tbody>
</table>

Table 1 Recommendations for daily practice in patients with suspected infection the Intensive Care Unit (ICU) based on expert opinion of the authors.
Recommended Future Research Strategies and Directions

Development of a novel, point-of-care test that accurately identifies both a host response to infection and the causative pathogen to assist in the reliable diagnosis and treatment of sepsis. A tool that reliably differentiates between infection and non-infectious clinical mimics would also be of importance in other studies that aim to identify the value of other interventions (e.g. fluids, early vasopressors) in patients with sepsis.

Controlled trials that compare early empiric therapy to a more conservative or delayed antibiotic strategy in ICU subpopulations (e.g. burns, trauma, febrile neutropenic patients).

All studies investigating the effectiveness of various treatment strategies in sepsis should report on: the appropriateness of antibiotics given; time to source control and effectiveness of source control; and how/whether infection was confirmed.

Studies to evaluate whether antibiotics are needed at all in conditions where adequate source control has been achieved (i.e. removal of infected catheters with associated low virulence organisms)

Table 2 Recommended future research strategies and directions aimed at preventing antibiotic overuse in the ICU
Figure 1 Do I Need to Give Antibiotics?

Transparency Statement: Dr. DE WAELE reports other from Bayer, other from Pfizer, other from MSD, other from Grifols, other from Accelerate, outside the submitted work.

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Contribution: KJD performed the literature search and contributed to manuscript preparation, editing and revisions. JDW, KBL, PNAH, and JL contributed to the manuscript preparation, editing, and revisions.
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**Do I Need to Give Antibiotics?**

<table>
<thead>
<tr>
<th>YES</th>
<th>WATCH and WAIT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient has a proven bacterial infection (i.e. a known pathogen, cultured at a significant level, that is likely to be the cause of the clinical presentation)</td>
<td>The undifferentiated febrile patient who is not hypotensive</td>
</tr>
<tr>
<td>The patient’s presentation is consistent with an immediately life-threatening infection (e.g. suspected bacterial meningitis, meningococcal sepsis)</td>
<td>The patient with a colonised catheter with a low virulence organism</td>
</tr>
<tr>
<td>The patient is hypotensive due to suspected infection</td>
<td>The patient with a ventilator-associated condition (VAC(^f))</td>
</tr>
</tbody>
</table>

*Watch and Wait: Close monitoring of the patient in an high-dependency or intensive care setting for signs of deterioration whilst further investigations and attempts at source identification and control are carried out.

\(^f\)VAC: An increase in the minimum PEEP during a 24-hour period of 3cm H\(_2\)O or an increase in the minimum FiO\(_2\) during a 24 hour period of 20%, after a period of 48 hours of stable ventilator settings