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LESS IS MORE

Is prophylaxis worse than treatment in the ICU?

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Prophylaxis, an ancient practice in medicine and healthcare [1], has become a victim of its own success. It is now intrinsically rooted in medical behavior and stands out as a significant example of framing bias in patient care, i.e., a tendency to selectively display and promote positive aspects of an idea [2]. Most medical conditions are considered ominous, so prophylactic strategies are considered a priori good [1]. By avoiding disease, prophylaxis sounds better than cure. This rationale is present in several reports on the effects of prophylactic treatments, which use optimistic jargon to compel the reader, including magnification of the problem to be prevented, inappropriate measurement of adverse events, quoting the number of lives saved, number of events avoided, and numbers needed to treat [3–6]. It is uncommon to see the same focus on the direct harms of prophylaxis. These are rarely adequately reported, and uncertainty is not always acknowledged. Indirect harms, including those that affect patient care by draining workforce time or increasing costs, are even less frequently reported. Ventilator bundles to prevent adverse events associated with mechanical ventilation—which are mostly comprised of low-quality evidence interventions—is for example very time consuming [7]. However, this does not mean that all prophylaxis is useless. We perform many simple prophylactic actions in daily clinical practice, i.e., fixation of devices, tubes, drains, and catheters, communication with patients and relatives, hand washing, and cleaning of rooms. The benefits of such prophylactic intervention may not always be obvious, but they often add value to patients, relatives and society.

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The benefit of avoiding a specific condition depends on its incidence, the risks associated with it, and the risks associated with the treatment of that condition [8, 9] (Fig. 1). Some prophylactic strategies that aim to prevent common (high incidence) conditions, that have low intrinsic risks, and which potentially can avoid a serious condition may result in an overall improved outcome. For example, it has been suggested that a cheap and low-risk intervention like aspirin can be effective in the prevention of cancer—a common and costly healthcare problem [8]. In other circumstances, the condition to be barred may be rare, but costs of prophylactic treatment may still be justifiable if the condition is costly and clinically relevant to patients [9] (Fig. 1). Other interventions with the opposite combination of these factors may result in a worse overall outcome. This may, however, not be true in a complex scenario with multiple conditions of questionable attributable risks flooded with conflicting therapies, such as many interventions in the intensive care unit (ICU). Evaluating net benefit is cumbersome and many pieces of the required information are frequently missing. For example, proton-pump inhibitors (PPIs) can effectively reduce the risk of gastrointestinal bleeding in critically ill patients [10], but it may be more uncertain if the net effect is beneficial given costs and risks of side effects. All information required for a cost-utility analysis, which should drive decisions for prophylaxis, are context-sensitive. In ICUs, this is even more prominent.

Due to negativity bias [11] and the low frequency of many complications/side effects/serious adverse events, and their multifactorial etiology, physicians struggle to estimate the true effect of a prophylactic intervention. If stress ulcers occur in a critically ill patients not using PPI, physicians will tend to attribute the bleeding exclusively to lack of PPI use (anchoring) [2], despite many other risk factors being involved. This will reinforce overzealous use

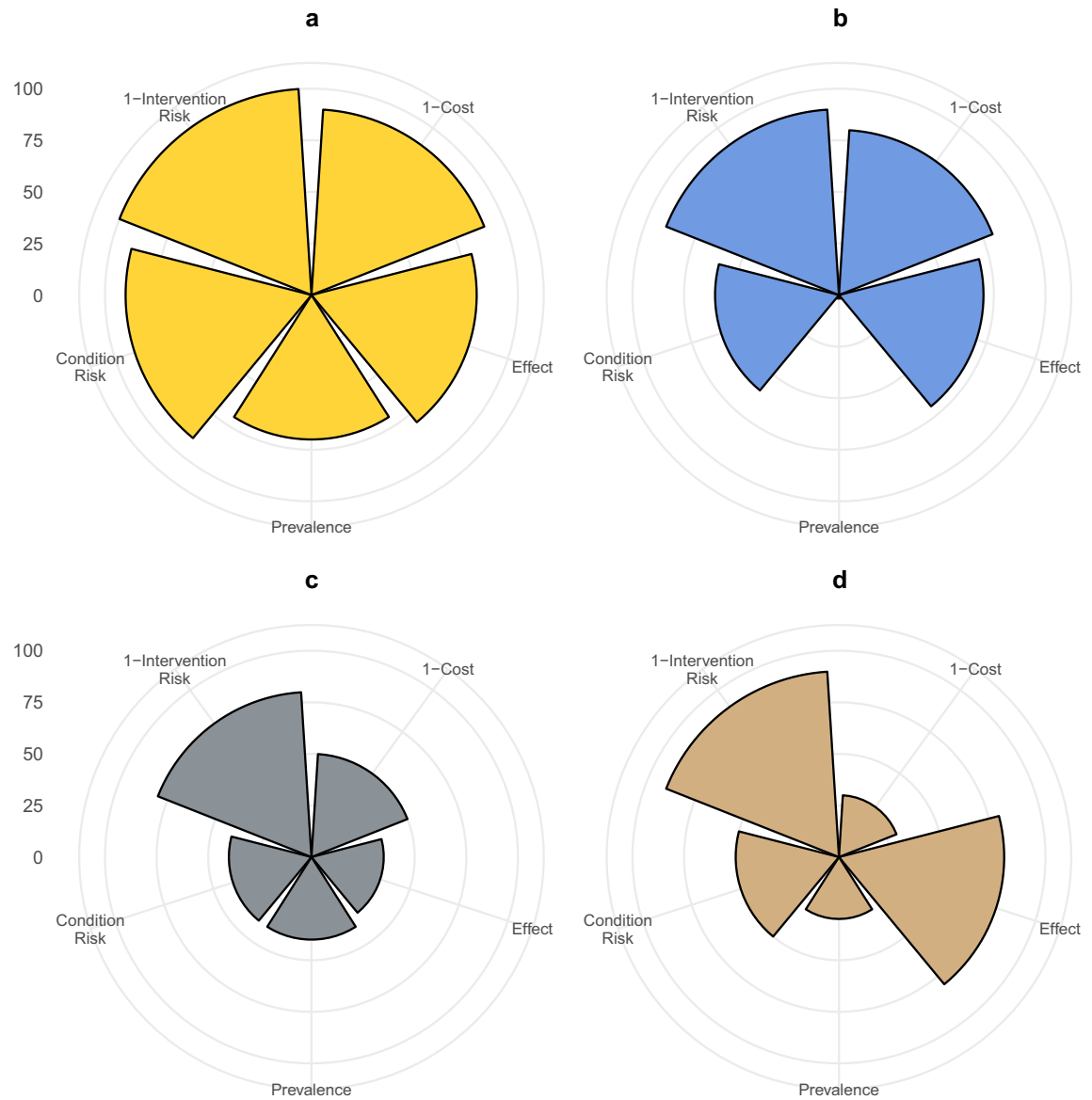

Fig. 1 An illustration of the factors that must be considered re prophylactic interventions, i.e., costs of the intervention, prevalence of the condition to be avoided, effectiveness of the prophylactic intervention, risk of the condition, and risk of the prophylactic intervention must all be considered. In the spider plot, we show four different scenarios. The complement value of cost and risk of the prophylactic intervention were used for clarity, therefore the higher the totals are in the plot, the higher the probability that the prophylactic intervention is useful. **a** An outstanding prophylactic intervention with low cost, low risk, and a good effect in avoiding a condition that has high prevalence and that is associated with high risks. Example: tobacco control, sedation in ICU. **b** A low-risk and cheap intervention which is used to avoid a rare complication which is associated with high risk. Example: prophylactic antibiotic before dental procedures in patients with prosthetic valves. **c** A low-risk, high-cost intervention which has a low/moderate effect to prevent a relatively common condition which may have serious consequences for the patient. In this situation, careful consideration of cost-effectiveness is warranted. Example: intermittent mechanical compression for deep venous thrombosis prophylaxis, endotracheal tubes with supraglottic aspiration for ventilator-associated pneumonia prevention. **d** A medium-cost effective prophylactic treatment which acts upon a low prevalence condition but has a very good effect. Example: pre-exposure HIV prophylaxis

of prophylactic interventions and blur critical appraisal of future clinical evidence.

Other specific factors pertinent to ICUs are also worthy of mention. First, the incidence and "true" risk of the condition we want to prevent is usually unknown. The incidence of many conditions in critically ill patients is largely unknown and has significant regional differences, hampering the generalizability of studies on prophylaxis

[12]. In the SUP-ICU trial, stress ulcer prophylaxis decreased GI bleeding without an identifiable effect on mortality [10]. This may suggest that the prevented condition has a low (at least low enough not to be identifiable) impact on mortality. Other conditions, such as ventilator-associated pneumonia, may have a very low attributable mortality [13], and unsurprisingly strategies that aim at decreasing ventilator-associated pneumonia have not consistently succeeded in improving overall outcome [14]. Additionally, these conditions sometimes suffer from even more pressing issues, such as difficulties in diagnosing and clashes between diagnostic criteria [15]. Even in a hypothetical scenario when we can definitively prevent an ICU event, there is no certainty that what has been prevented was indeed clinically relevant. Second, prophylaxis in critically ill usually means adding something. The most effective prophylactic strategies are those based on avoiding a harmful exposure (tobacco, for example [16]) or those that remove an intervention (such as sedation) [17]. In the ICU, prophylaxis is usually performed by changing routine care by adding something, such as medication, bed position, or devices such as intermittent compression for venous thromboembolism prevention. All of these interventions have their own inherent risks and drive attention away from other perhaps more pressing needs [7]. Furthermore, adding interventions tends to make clinical practice even more complex, and increases workload, the risk of drug–drug interactions and side effects [18, 19].

Idolatry of prophylaxis has inconsistent benefits for patients, may cause harm in some settings, and give a false sense of safety and quality of care in ICU patients. For some situations, the problems resulting by use of a prophylactic intervention may be greater than treating the preventable condition. There is no simple solution to this complex scenario. From one end, physicians must look at current prophylactic treatments with skepticism. This is hard, as many prophylactic treatments are so commonplace that the evidence required to de-implement them from clinical practice will need to be much stronger than the evidence that was originally used to justify their adoption in the first place. This *endowment effect* occurs daily for many medical treatments and is a barrier for clinical research and evidence-based medicine [19].

In summary, we need more patient-centered outcome research, focusing on preventing conditions which matter to patients and relatives, rather than things of interest to researchers and physicians. By avoiding unnecessary prophylactic interventions, we can rest assured that patient harm is minimized. We also need to communicate and discuss that prophylaxis may not always be beneficial, and sometimes benefits may even be offset by side effects and harms.

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Compliance with ethical standards

Conflicts of interest
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