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Multi-resistant *Acinetobacter baumannii* emergence associated with healthcare infections: Meta-analysis

Emergência de *Acinetobacter baumannii* multirresistente associado a infecções relacionadas à assistência à saúde: Metanálise

Aparición de *Acinetobacter baumannii* multi-resistente asociada con infecciones relacionadas con la asistencia sanitária: Metaanálisis

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Abstract

The high resistance to antimicrobials has made hospitals a potentially dangerous environment for the development of HAIs, especially when associated with multi-resistant bacteria such as *A. baumannii*. The work aimed to evaluate the incidence of multidrug-resistant *Acinetobacter baumannii* described in the literature through a meta-analysis. A meta-analysis of a qualitative and quantitative nature was carried out in which original articles and review articles that presented data on the occurrence and existence of multidrug resistance in *Acinetobacter baumannii* were evaluated. The Scientific Electronic Library on Line (SciELO) and Medical Literature Analysis and Retrieval System Online (Pubmed / MEDLINE) databases were consulted using the descriptors "*Acinetobacter baumannii*," "multi-resistance," "IRAS," "incidence." Most studies were carried out in 2018. In general, most studies were cross-sectional 85.00% (n = 17) and cohort 15.00% (n = 3). In the selected studies, 5877 cases were reported, of which 3544 corresponded to multi-resistant species of *Acinetobacter*. The cumulative prevalence ratio corresponded to 0.603 with a 95% confidence interval [0.590 to 0.615]. The analysis of the temporal trend of the Ratio of the prevalence of multidrug-resistant *Acinetobacter baumanni* according to the year of the selected studies indicated that the PR suffered a decline in 2009 and 2013 and a new tendency to increase from 2015 and suffered small fluctuations until 2019, the trend did not show significant (R^2 = 0.0772). Therefore, the MDR profile is worrying, given the currently available therapeutic alternatives.

Keywords: *Acinetobacter baumanni*; Resistance; MDR.

Resumo

A elevada resistência aos antimicrobianos tornou os hospitais um ambiente potencialmente perigoso para o desenvolvimento de IRAS, principalmente quando associada a bactérias multirresistentes tais como *A. baumannii*. O trabalho teve como objetivo avaliar a incidência da *Acinetobacter baumannii* multirresistente descrita na literatura através de uma metanálise. Foi realizada uma metanálise, de natureza quali-quantitativa na qual foram avaliados artigos originais e artigos de revisão que apresentassem dados sobre a ocorrência e existência da multirresistência em *Acinetobacter baumannii*. Foram consultadas as bases de dados

Scientific Eletronic Library on Line (SciELO) e Medical Literature Analysis and Retrieval System Online (Pubmed/MEDLINE) mediante o emprego dos descritores "*Acinetobacter baumannii*", "multiressistência", "IRAS", "incidência". A maioria dos estudos foi realizado em 2018. No geral, a maioria dos estudos eram transversais 85,00% (n = 17) e coorte 15,00% (n= 3). No conjunto de estudos selecionados foram relatados a ocorrência de 5877 casos, dos quais 3544 corresponderam a espécies multirresistente de *Acinetobacter*. A Razão de prevalência cumulativa correspondeu a 0,603 com um intervalo de confiança 95% [0,590 a 0,615]. A análise da tendência temporal da Razão da prevalência *de Acinetobacter baumanni* multirresistente segundo o ano dos estudos selecionados indicou que a RP sofreu um declínio em 2009 e 2013 e nova tendência de aumento à partir de 2015 e sofreu pequenas oscilações até 2019, a tendência não se mostrou significativa (R^2 = *0,0772*). Logo, o perfil de MDR é preocupante frente as alternativas terapêuticas atualmente disponíveis.

Palavras-chave: *Acinetobacter baumanni;* Resistência; MDR.

Resumen

Una alta resistencia a los antimicrobianos ha convertido a los hospitales en un entorno potencialmente peligroso para el desarrollo de infecciones relacionadas con la salud (HAI), especialmente cuando se asocian con bacterias multi-resistente como *A. baumannii*. El trabajo tuvo como objetivo evaluar la incidencia de *Acinetobacter baumannii* multi-resistente descrito en la literatura a través de un metaanálisis. Se realizó un metaanálisis, de carácter cualitativo y cuantitativo, en el que se evaluaron artículos originales y artículos de revisión que presentaban datos sobre la ocurrencia y existencia de multi-resistencia en *Acinetobacter baumannii*. Se consultaron las bases de datos Scientific Electronic Library on Line (SciELO) y Sistema de Análisis y Recuperación de Literatura Médica en Línea (Pubmed / MEDLINE) utilizando los descriptores "*Acinetobacter baumannii*," "multirresistência," "IRAS," y "incidência." La mayoría de los estudios se realizaron en 2018. En general, la mayoría de los estudios fueron de corte transversal 85,00% (n = 17) y de cohorte 15,00% (n = 3). En el conjunto de estudios seleccionados, se notificaron 5877 casos, de los cuales 3544 correspondieron a especies multi-resistentes de *Acinetobacter*. La razón de prevalecía acumulada correspondió a 0,603 con un intervalo de confianza del 95% [0,590 a 0,615]. El análisis de la tendencia temporal de la Razón de la prevalecía de *Acinetobacter baumanni* mult-iresistente según el año de los estudios seleccionados indicó que la RP sufrió una caída en 2009 y 2013 y una nueva tendencia a aumentar desde 2015 y sufrió pequeñas fluctuaciones

hasta 2019, la tendencia no mostró signifiancia (R2 = 0.0772). Por tanto, el perfil de MDR es preocupante ante las alternativas terapéuticas disponibles en la actualidad.

Palabras clave: *Acinetobacter baumanni*; Resistencia; MDR.

1. Introduction

Health Care Related Infections (IRCH) are defined as infections acquired after the patient's admission to the hospital environment. Usually 72 hours after admission, which may occur during hospitalization or after discharge, related to hospital procedures and to the period of hospitalization itself. In the case of the presence of infection since admission, IRAS is considered when there is a worsening or isolation of another pathogen in the same topography (ANVISA, 2017a).

The development of IRCH often results in several losses, such as more extended hospitalization, the economic impact on the public health sector, higher mortality, and advancement in bacterial resistance (Leoncio et al., 2019). Among the losses cited, bacterial resistance has gained much prominence, and its most frequent pathogens are associated with IRAS were grouped in an acronym and called "ESKAPE" (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp)* (Araújo & Pereira, 2018).

In 2017 the World Health Organization (WHO) published a list of the primary pathogens associated with antibiotic resistance in the world, highlighting the immediate need to promote research and development of new drugs to confront multidrug resistant bacteria that pose the greatest threat to human health. Among them are the *Acinetobacter baumannii bacteria* of the *Moraxellaceae* family, genus *Acinetobacter,* cocobacilars, gram-negative, aerobic, non- fermenting glucose, positive catalase, and negative oxidases (PAHO, 2017).

The high resistance to antimicrobials has made hospitals a potentially dangerous environment for IRCH development, significantly when associated with multi-resistant bacteria such as *A. baumannii* (Dalmasio, 2018). Several mechanisms of resistance to different antimicrobials have been described for the genus Acinetobacter, among them the enzymatic mechanism (β- lactamases), which degrade antibiotics by the action of enzymes such as cephalosporinases (class A of Ambler Ex: AmpC and ESBL- β-lactamases Extended Spectrum) (Ranjbar, et al., 2018). Also, the metalo- β-lactamases (class B of Ambler) and

oxacillinases (class D of Ambler) that have activity against carbapenem antibiotics (Chagas, 2015).

Other resistance mechanisms include multidrug efflux pumps that decrease the concentration of antibiotics in the periplasmic space (Vashist et al., 2011). In addition to changes in affinity for penicillin-binding proteins (PBPs) and decreased permeability of external membranes (Pagano, et al., 2016). Individuals admitted to the intensive care unit (ICU), carriers of HIV/AIDS, presence of invasive devices, and excessive use of antimicrobials are near related to the emergence of bacterial resistance (Roberts, et al. , 2009).

Strategies such as those recommended by WHO in 2008 reinforce the central moments in which health professionals must perform hand hygiene, necessary action for patient safety. Besides, WHO, together with the member countries of the United Nations (UN), including Brazil, have stimulated the elaboration of individual Plans to combat antimicrobial resistance around the world. This proposal resulted in 2017 in the launching of the document entitled "National Guideline for the Elaboration of a Program for the Management of the Use of Antimicrobials in Health Services," which contains actions for the combat and containment of microbial resistance according to the national reality (ANVISA, 2017b).

Even in the face of the evolution of research for the development of several antimicrobials classes, these have been presenting failures in the combat due to the constant mutations of bacterial strains and increase of resistance mechanisms (Gomes, et al, 2014). Given this, the early detection, control, and prevention of IRCH are fundamental measures for reducing outbreaks of *A. baumannii.* (Paula, et al. , 2017). Considering the high rates of IRAS associated with this species in recent years, the work aimed to evaluate the incidence of multi-resistant *A. baumannii* described in the literature through a meta-analysis.

2. Methodology

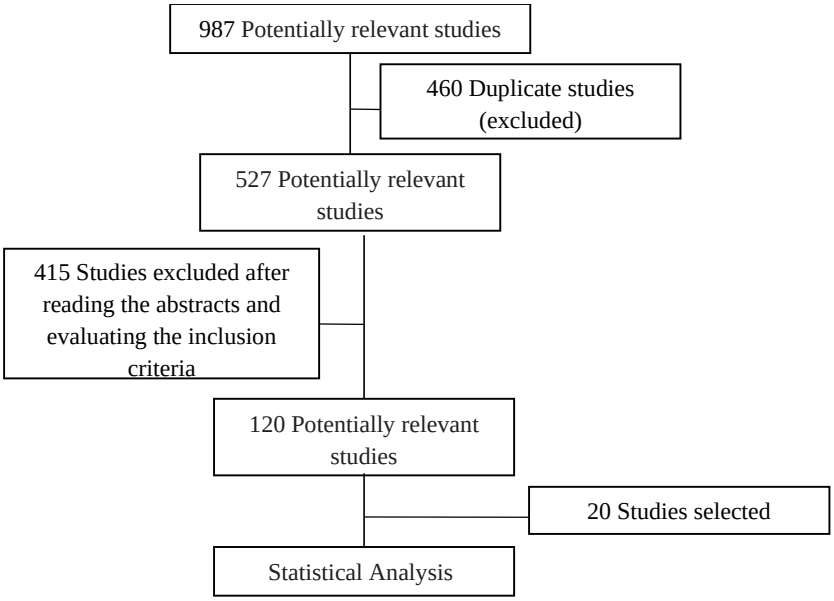
For this study, a meta-analysis of a quali-quantitative nature was carried out in which original articles and review articles presenting data on the occurrence and existence of multi-resistance in *A. baumannii* were evaluated. According to the scientific research elaboration manual proposed by Pereira et al. (2018), the data were collected by simple random sampling. The Scientific Electronic Library on Line (SciELO) and Medical Literature Analysis and Retrieval System Online (Pubmed/MEDLINE) databases were

consulted using the descriptors "*Acinetobacter baumannii*," "multi-resistance," " IRCH," "incidence."

As inclusion criteria, national and international articles were selected, available in full, published in Portuguese or English, between 2003 and 2019. The exclusion criterion was duplicity, non-availability in full, and articles that, despite presenting the selected descriptors, the scope did not present a direct relation to the proposed theme and the absence of absolute data necessary for meta-analysis. Finally, considering these aspects, 33 articles were selected for analysis.

Considering the likely heterogeneity among observational studies, an effects model was applied to calculate 95% confidence intervals (CIs). The Confidence Interval Calculator prepared by Herbert (2013) was used to calculate the CI and Prevalence Ratio (RP) of multi-resistance. When the prevalence was reported for several years that extended for more than one year, the study was included in the period that captured the most updated data. Only studies that reported the year the study was conducted were included in the meta-analysis. To demonstrate the distribution of multi-resistance among *A. baumannii*, a

Figure 1 - Flowchart of the articles' selection process for the integrative literature review.



Source: Authors.

forest plot was created using Microsoft Excel® 2013. Below is a flowchart of the articles' selection process for the integrative literature review (Figure 1).

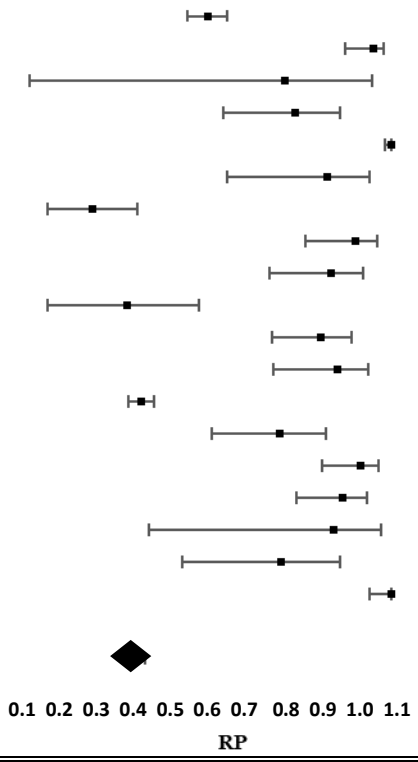
3. Results

A total of 987 records were identified in the databases, of which 20 studies were included for analysis (Table 1). Most of the excluded works were research articles, followed by short reports, only abstract for annals, and letter to the editor. We selected data published in Latin America, Europe, and the Middle East, with works predominantly published in Brazil (85%).

Most studies in Table 1 were conducted in 2018, and the duration of the studies varied from 1 to 10 years. There were variations in susceptibility testing methods, including automated methods, such as VITEK, and other tests, including E-test, diffusion disk, and broth microdilution. In general, most studies were 85.00% (n = 17) transversal and 15.00% (n = 3) cohort.

Table 1 - Incidence and prevalence ratio of multidrug-resistant Acinetobacter described in the selected literature.

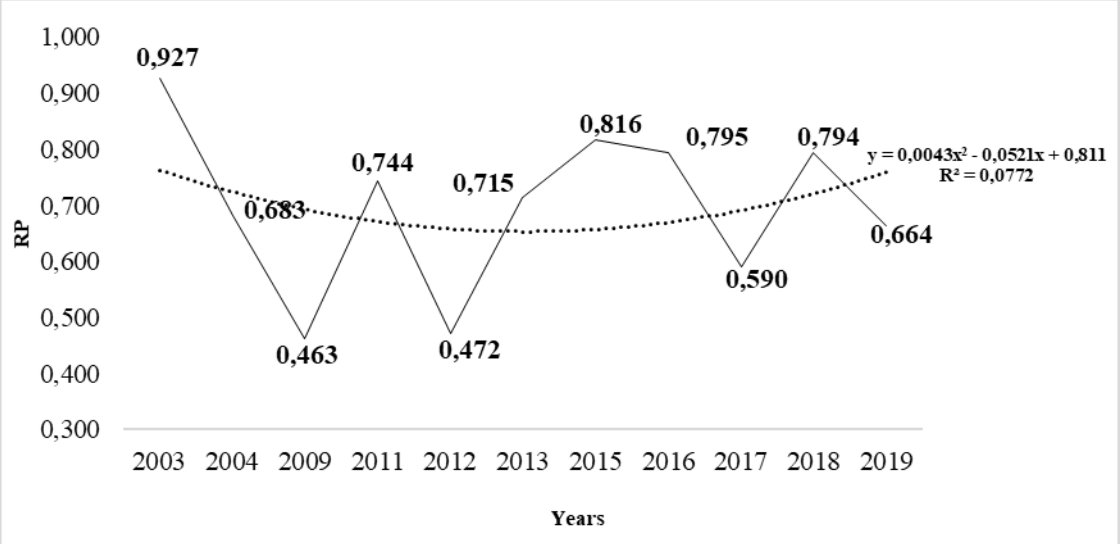
Authors	(n)	MDR	RP	IC95%
Tognim, et al., 2004	826	590	0,714	0,683-0,744
Kiffer, et al., 2003	137	133	0,971	0,927-0,989
Lima, et al., 2019	006	005	0,833	0,436-0,970
Gomes, et al., 2016	060	051	0,850	0,739-0,919
Sousa, 2018	361	361	1,000	0,989-1,000
Guimarães, 2011	030	027	0,900	0,744-0,965
Borouman, 2009	191	102	0,534	0,463-0,603
Nóbrega, et al 2013	072	068	0,944	0,866-0,978
Godoy, 2012	064	058	0,906	0,810-0,956
Viana, 2013	063	037	0,587	0,464-0,700
Asadollahi et al., 2013	100	089	0,890	0,814-0,937
Leão, 2015	059	054	0,915	0,816-0,963
Silva, 2017	2292	1398	0,610	0,590-0,630
Lima, 2018	069	057	0,826	0,720-0,898
Romanin *et al*, 2019	103	098	0,951	0,891-0,979
Genteluci, 2016	092	085	0,924	0,851-0,963
Araújo *et al*, 2018	011	010	0,909	0,623-0,984
Mota *et al*, 2018	035	029	0,829	0,673-0,919
Gholami, *et al*, 2018	110	110	1,000	0,966-1,000
Gales, 2012	1196	182	0,152	0,133-0,174
Cumulativa	5877	3544	0,603	0,590-0,615



Legend: n = incidence of Acinetobacter; MDR = incidence of multidrug-resistant Acinetobacter; PR = Prevalence Ratio; 95% CI = confidence interval. Source: Authors.

Table 1 reveal that in the selected studies, 5877 cases were reported, of which 3544 corresponded to multi-resistant species of *A. baumanni*. The cumulative prevalence ratio corresponded to 0.603 with a 95% confidence interval [0.590 to 0.615]. Figurate 2 illustrates analysis of the time trend of the Prevalence Ratio (PR) of *A. baumanni* multidrug-resistant (MDR) according to the year of the selected studies indicated that PR suffered a decline in 2009 and 2013 and a new tendency to increase from 2015 and suffered small oscillations until 2019, the trend did not show significant (*R2 = 0.0772*).

Figure 2 - Tendence of the Ratio of the average prevalence of multi-resistant Acinetobacter baumanni according to the year of the selected studies.



Source: Authors.

4. Discussion

Multidrug-resistant (MDR) is considered that microorganism resistant to at least one agent in three or more classes of antimicrobial agents (Oliveira & Damasceno, 2010). In the present study, out of 20 selected studies, 13 (65%) of them identified strains of *A. baumannii* with MDR profiles. Besides, all studies detected 5877 samples of *Acinetobacter* in the hospital environment, and 60% (n=3544) of the samples presented MDR, which is worrying given the therapeutic alternatives currently available.

Godoy's study (2012) conducted in the central-western region of Brazil, states that the leading cause of the high MDR rate of *A. baumannii* in the ICUs studied is directly linked to the widespread use of antimicrobials in the population assessed, with the use of

more than two classes of antibacterial in 68% of cases. Besides the abusive use of antimicrobials, the resistance to these agents is related to indifferent prescriptions to the current evidence-based methods, and the lack of global epidemiological surveillance (Gurgel & Carvalho, 2008).

Class D carbapenemases or oxacillinase (OXA) can hydrolyze the beta-lactam ring of carbapenems (Chen et al., 2014). The high resistance to carbapenems found in this study exemplifies the increasing loss of sensitivity of *A. baumannii* to these drugs, which is mostly due to the presence of oxacillininses (OXA) and which are identified by molecular techniques such as Polymerase Chain Reaction (PCR). In the studies of Wales et al. (2012), Gomes et al. (2016), Asadollahi et al. (2013), Romanin et al. (2019), Genteluci et al. (2016), and Gholami et al. (2018), genetic subgroups such as *blaOXA-23 which is* acquired through plasmids and OXA-51-like which is a gene formed by the intrinsic pathway of *A. baumannii* were identified. (Higgins, et al., 2013).

The study by Genteluci (2016) was relevant in identifying high rates of OXA isolates, in which all samples 100% (n=92) had the *blaOXA-51 gene* and 92.3% (n=85) had the *blaOXA- 23* gene.

Currently, polymyxins have been considered the only option for treating severe infections caused by *A. baumannii* MDR, which generates concern due to the scarcity of therapeutic alternatives (Pogue, 2015). The generalized reintroduction of this antibiotic and its non-rational use may trigger adverse reactions such as nephrotoxicity and neurotoxicity, which led to its abandonment (Arroyo, et al., 2009). Although currently considered the only therapeutic option, the intensive use of polymyxins has already shown the emergence of resistant *A. baumannii* samples, with resistance rates of 40.7% in Spain and 30.6% in South Korea (Ko, et al., 2007).

In studies by Gomes and Genteluci et al. (2016), both conducted from samples collected from patients treated in the public health network of Rio de Janeiro, in different institutions, through the performance of antibiogram identified resistance to polymyxins in most samples 75 (n=92) and 41 (n=60) respectively. The absence of susceptibility to the antibiotic was identified in polymyxin concentrations below 4 μg/mL, and CIM (minimum inhibitory concentration) ≥ 4 μg/mL. According to the National Health Surveillance Agency, resistance to polymyxins must be monitored continuously, and its detection reported to health authorities according to the National Plan for the Prevention and Control of Microbial Resistance in Health Services (ANVISA, 2017a).

In Leão (2015), performed from the samples of 59 patients in the ICU of a Clínicas

de São Paulo hospital, it was shown that 81% (n=48) of patients with bacteremia by *A. baumannii* developed septic shock. Moreover, about 50% of the patients had a median survival for up to two days after diagnosing infection by this microorganism. It is noted that the direct consequences of bacterial resistance are the high costs generated by hospitalization (bed, drugs, etc.), polyantibiotic therapy resulting in greater chances of drug interactions, and immeasurable disorders (suffering, death, pain) (Ballot, et al. , 2012).

The clinical microbiology laboratory plays a guiding role in the correct prescription of antimicrobials because it isolates, identifies, and determines the sensitivity profile to antimicrobials of pathogens causing infections (ANVISA, 2017b). Moreover, the pharmacy sector's participation is essential for the fulfillment of the stages of pharmaceutical assistance, which aims to ensure the population's access to quality drugs, contributing to rational use (Ministry of Health, 2007). The pharmacy sector also participates in the triage (review) of medical prescriptions, which reduces possible errors of dose or therapeutic indication (Silva, 2012). Besides, the clinical pharmacy assists in therapeutic monitoring (dose adjustment based on plasma concentration), optimization of dosage according to the clinical characteristics of the patient (weight, renal function), the etiological agent, and the pharmacokinetic and pharmacodynamic characteristics of the drug (Santos, et al. , 2019).

Some articles selected here stand out for the dissemination of strategies in the confrontation and reduction of IRAS by *A. baumannii* as Modesto and Brito (2019), which claim to be an effective measure to promote the decolonization of empirical therapy, i.e., opting for therapy with the use of reduced spectrum antimicrobials, even when treatment with broad-spectrum antibiotics has begun, and they show positive results. Viana (2013) emphasizes the fundamental role of measures such as hygiene of the hands, minimizing the risks of infection associated with the use of procedures, equipment, medical devices, and standard precautions.

Veloso, Campelo e Sá (2017) ratify that for the rational use of antimicrobials, it is essential to adopt educational and restrictive measures, such as continued education of prescribers, the requirement to fill out a form for the supply of restricted antimicrobials, and actions that limit the interference of the pharmaceutical industry. Therefore, in front of the limited therapeutic alternatives for the treatment of IRAS by *A. baumanni* MDR, we conclude that it shows the necessary development of new drugs.

5. Conclusion and Suggestions

It is possible to conclude that *Acinetobacter baumannii* multi-resistant presents a substantial incidence, which represents a worrying public health problem since it contributes to an increase in mortality and costs. Among the study's limitations, we mentioned the small number of randomly selected articles, which may or may not have underestimated or overestimated the data.

Among the suggestions for the reduction of the incidence of multi-resistant species of *A. bauumannii*, we recommend the implantation of a program of management of the use of antimicrobials in health services, which involves a set of actions destined to its control, which include the excellent practices of dilution, conservation and administration, besides the audit and monitoring of prescriptions, education of professionals and patients, assuring optimal therapeutic results with minimum potential risk.

As a tool, the Brazilian Ministry of Health instituted the National Program for Prevention and Control of Health-related Infections as a tool to guide professionals. The document has produced guides for several actions, such as surveillance and monitoring of microbial resistance, early identification, patient management flows, biosafety standards for professionals and patients, guidelines for collecting and forwarding samples to Central Public Health Laboratories (LACEN).

This study indicates that the characteristics of MDR are similar in the multiple published studies; however, new work must be carried out to expand scientific knowledge on the subject.

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