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The Utility of Procalcitonin as a Biomarker to Limit the Duration of Antibiotic Therapy in Adult Sepsis Patients

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Abstract

Introduction: With rising global antibiotic resistance, stewardship programs aimed at controlling multi-drug resistant (MDR) pathogens have begun to gain acceptance. These programs stress appropriate antibiotic selection, dosage and duration. A growing literature suggests serum procalcitonin (PCT) levels may be useful in guiding antibiotic duration and de-escalation. This report sought to evaluate the evidence-based data available from prospective randomized controlled trials (RCT) on the role of PCT in guiding reductions in antibiotic duration in adult sepsis patients. Methods: A comprehensive search of all published prospective RCT(s) on the use of PCT as a tool for guiding antibiotic therapy in adult sepsis patients was conducted using PubMed, Medline Plus and Google Scholar (2007-2013). Keywords searched included, "procalcitonin", "sepsis-therapy", "sepsis biomarker", "antibiotic duration", "drug de-escalation", and "antimicrobial stewardship". Results: Four RCT(s) involving 826 adult sepsis patients have evaluated the role of serum PCT levels to guide criteria for cessation of antibiotic therapy based either on specific PCT levels or PCT kinetics. Bouadma *et al.* (N = 621) stopped antibiotics when the PCT concentration was <80% of the peak PCT value, or the absolute PCT concentration was <0.5 μg/L. The PCT arm showed a 2.7-day reduction in antibiotics. Schroeder *et al.* (N = 27) discontinued antibiotics if clinical signs of infection improved and the PCT value decreased to <1 ng/mL or to <35% of the initial value within three days. The PCT arm had a 1.7-day reduction in antibiotics. Hochreiter *et al.* (N = 110) ceased antibiotics when the PCT decreased to <1 ng/mL, or to 25% - 35% of the initial value over three days if the value was >1 ng/mL. The PCT arm showed a 2-day reduction in antibiotics. Finally, Nobre *et al.* (N = 68) stopped antibiotics when PCT levels decreased by 90% or more from the initial value, but not prior to Day 3 (if baseline PCT measured <1 μg/L) or Day 5 (if baseline PCT measured ≥1 μg/L). The PCT arm showed a 4-day reduction in antibiotics. Overall, reduction of

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PCT levels to 10% - 35% of the initial concentration, to <80% of the peak PCT value, or to an absolute PCT value of <1 μg/L warranted antibiotic discontinuation 1.7 to 4 days earlier. No study reported a significant difference in mortality between the PCT arm and the control arm ($p < 0.05$). Conclusions: PCT-guided early cessation of antibiotic therapy in adult sepsis patients is associated with a significant decrease in antibiotic days, with no effect on overall mortality. Measurement of serum PCT levels may have a role in antimicrobial stewardship programs aimed at limiting antibiotic therapy duration, decreasing the selective pressure on drug-resistant bacterial strains and reducing hospital costs.

Keywords

Procalcitonin, Sepsis Therapy, Sepsis Biomarker, Antibiotic Duration, Antibiotic De-Escalation, Antimicrobial Stewardship

1. Introduction

Sepsis, a medical condition characterized by systemic inflammation in the presence of an infectious process (**Table 1**), has burdened inpatient facilities for decades with mortality rates ranging from 27% to 54% [1] [2]. Sepsis represents a serious public health threat to inpatient safety on a global scale. Recent Healthcare Cost and Utilization Project (HCUP) statistics have shown that septicemia, the sixth most frequent primary inpatient diagnosis in 2009, and hospital stays for septicemia overall increased by 153% between 1993 and 2009 [3] [4]. Hospital stays for sepsis incurred a healthcare cost of $15.4 billion in 2009, with an average annual cost growth of 11.9% per year between 1997 and 2008 [4] [5]. The increases in sepsis-related hospitalization, associated with rising costs of therapy make it incumbent upon medical professionals to develop new cost-reduction strategies while simultaneously achieving optimal clinical outcomes.

In the modern antibiotic era, treatment protocols for sepsis necessitate the rapid institution of broad-spectrum antibiotics, often empirically, as delayed antimicrobial therapy is associated with both increased morbidity and mortality [1] [6]-[10]. Harbarth *et al.* [6] reported that patients treated with inappropriate initial antibiotic therapy had a 39% 28-day mortality, while those who received appropriate treatment had a 24% mortality rate, demonstrating that inappropriate therapy was independently associated with increased mortality (OR = 1.8; 95% CI, 1.2 - 2.6). Kumar *et al.* [8] described a strong association between delayed administration of antibiotics and in-hospital mortality in septic patients with hypotension (OR = 1.119 per hour of delay; 95% CI, 1.103 - 1.136),

Table 1. The American college of chest physicians and the society of critical care medicine criteria for diagnosis of sepsis [47].

Parameter	Value
Body temperature	• <36˚C (97˚F); or • >38˚C (100˚F)
Heart rate	• >90 beats per minute
Respiratory rate	• >20 breaths per minute; or • Blood gas $PaCO_2$ < 32 mm Hg (4.3 kPa)
WBC count	• <4000 cells/mm^3 (4×10^9 cells/L); or • >12,000 cells/mm^3 (12×10^9 cells/L); or • >10% band forms (immature WBCs)
Infection	• Clinically suspected; or • Proven (by stain, culture, PCR)

Abbreviations: $PaCO_2$ = Partial pressure of arterial carbon dioxide, WBC = white blood cell, PCR = polymerase chain reaction.

noting proper administration within the first hour of hypotension was associated with 79.9% survival with a decrease of 7.6% per hour of delayed administration. However, while the recommendation for early antibiotics is supported by evidence-based data, the choice of which antimicrobial regimen to use as well as the duration is largely subjective, varying from practitioner to practitioner [11]. Thursky *et al.* [12] reported that controlling antimicrobial decision-making in the ICU using a computerized system (thereby defeating arbitrary drug regimen/duration choice) led to decreased use of carbapenems (OR = 0.61; 95% CI, 0.39 - 0.97), third-generation cephalosporins (OR = 0.58; 95% CI, 0.42 - 0.79) and vancomycin (OR = 0.67; 95% CI, 0.45 - 1.00), a 10.5% reduction in total antibiotic use, fewer microbial susceptibility mismatches (OR = 0.63; 95% CI, 0.39 - 0.98) and an increased frequency of de-escalation to narrow spectrum antibiotics. Arbitrary use of antibiotics has led to well-documented overuse, with anywhere from 22% to 65% of all hospital antibiotics being deemed inappropriate [13] [14]. Moreover, the lack of standardized therapy, paired with the indiscriminate use of antibiotics and a lack of significant oversight has resulted in serious implications on the cost of medical care [15]-[25]. More importantly, this trend has contributed to the global emergence of multi-drug resistant (MDR) bacterial strains [11] [12]. Finland *et al.* [26] documented the development of antibiotic resistance over the course of forty years (1935-1975), citing resistance in strains of *streptococcus* sp., *staphylococcus* sp. and other virulent organisms. Since then, several additional experts have reported a link between antibiotic use and the development of resistance, highlighting the importance of reducing the use of unnecessary antibiotics [27] [28].

More recently, the implementation of antimicrobial stewardship programs (ASPs) has garnered a great deal of interest in an effort to limit antibiotic use globally. The primary focus of ASPs are to assure appropriate antibiotic selection, dosage and duration [29], with the goals of minimizing selective pressure on bacterial strains and maximizing "clinical impact and longevity" of antibiotics [30]. ASPs, which stress appropriate custom-tailored therapeutic regimens on a per-patient basis [31], also aim to reduce healthcare expenditures [11] and adverse effects caused by prolonged antibiotic exposure [11] [32] [33]. The foundational precepts of ASPs were described as early as the 1990s, with a 1996 study by Goldmann *et al.* outlining a number of strategic goals aimed at optimizing antibiotics use [34]. Since then, studies by Apisarnthanarak *et al.* [35], Tseng *et al.* [36], Allerberger *et al.* [37] [38] and several others have described the successful international implementation of ASPs in Thailand, Taiwan and the European Union, with a recent report by George *et al.* [39] suggesting the institution of ASPs in ICU settings universally. It is anticipated that ASPs may ultimately become a cornerstone of efforts towards forestalling the growth of MDR pathogens [40].

Within ASPs themselves, there exist a number of potential strategic measures that may be utilized to reduce the incidence of MDR pathogens, including but not limited to antibiotic cycling (routine changes in antibiotic type at regular time intervals) [41]-[43], antibiotic mixing (random changes in antibiotic type on a continuous basis) [44] [45] and antibiotic de-escalation [30], though the effectiveness of each of these strategies is controversial [41]-[45]. A comprehensive literature review of antibiotic cycling by Kollef *et al.* [44] cited 7 reports defending its use, along with 2 studies presenting disputing data. The authors noted that current studies lack standardized prescribing practices, susceptibilities and outcome measures and are fraught with limitations and confounders, leading them to conclude that cycling is usually of limited use as a standalone strategy [44]. In contrast, a nine-year retrospective study by Sarraf-Yazdi *et al.* [41] concluded that cycling had kept steady or improved antimicrobial susceptibility profiles in gram-negative SICU infections. A review by Masterton *et al.* [45] cited 4 studies on cycling and mixing strategies and concluded that despite the potential for mathematical modeling to predict the effectiveness of mixing strategies, the role of such strategies continues to remain unclear. A similar review by Bal *et al.* [44] concluded that cycling and mixing may reduce resistance when used in conjunction with current approaches, but were not likely to have a significant impact when used individually.

Despite the conflicting data associated with antibiotic cycling and mixing strategies, other strategies such as antibiotic de-escalation have shown great promise [45]. Antibiotic de-escalation typically refers to narrowing or tailoring the breadth of antibiotic spectrum based on clinical response and laboratory measures, as well as early discontinuation of antimicrobial therapy when evidence of infection is no longer present (resulting in reduced therapy duration) [30]. To date, a number of trials supporting the use of de-escalation, specifically the reduction of antibiotic duration in common infections, have been published [40] [46]-[48]. Singh *et al.* [46] studied the use of short-duration antibiotic therapy in presumptive VAP patients, stopping antibiotics after 72 hours if the Clinical Pulmonary Infection Score was less than 6, and reported no difference in outcomes [resistance ($p = 0.017$), superinfection ($p = 0.017$), length of stay ($p = 0.0001$) or mortality ($p = 0.0001$)] when compared to patients receiving a full course of antibiotics. An RCT by Chastre *et al.* [47] demonstrated that appropriately treated venti-

lator-acquired pneumonia (VAP) patients only required 8 days of empirical antibiotics, compared to the recommended 14-day course with no difference in clinical outcomes. These conclusions were later confirmed in a similar study by Micek *et al.* [48]. Hayashi *et al.* [40] reviewed the use of antimicrobial therapy in community-acquired pneumonia (CAP), VAP, bacterial meningitis, pyelonephritis, infective endocarditis and intra-abdominal infections, citing a number of trials reporting reductions in antibiotic duration with comparable clinical outcomes. With evidence-based data validating the clinical benefit to decreased antibiotic duration, de-escalation strategies on the measurement of serum biomarker levels, such as procalcitonin (PCT) has now become a major area of research.

PCT is a novel biomarker with unique properties that make it a potential serum marker for directing the clinical management of sepsis. In healthy individuals, serum PCT levels remain below 0.1 ng/mL, but may increase a hundredfold or more in response to systemic bacterial infection [11]. PCT has been shown to rise rapidly after the onset of infection, starting to rise at 4 hours, with levels peaking between 8 and 24 hours [11]. Importantly, persistent elevation of PCT levels is only seen in bacterial infection and does not occur in viral infection or inflammatory processes [49]. Levels may increase in response to surgery, trauma or burns, but these increases are short-lived [49]. In the last decade, a growing literature pertaining to the value of PCT in sepsis diagnosis, prognostication and management has been explored [50]. Emerging research illustrates that PCT may even have merit extending beyond sepsis in the management of small bowel obstruction [51] [52], osteoarthritis [53], and necrotizing soft tissue infections [54]. This review critically evaluates all published literature with regards to the efficacy of PCT serum levels to guide antibiotic duration in septic adult patients, and discusses the strengths, limitations and future uses of PCT in sepsis therapy.

2. Methods

A comprehensive search of all published reports on the use of PCT levels to guide treatment of adult septic patients in both the intensive care unit (ICU) and non-ICU settings between 2007 and 2013 was conducted using PubMed and Google Scholar. The search focused on the value of PCT levels to guide antibiotic de-escalation, specifically reductions in duration of antibiotic administration. Keywords searched included, “procalcitonin”, “PCT”, “sepsis therapy”, “sepsis biomarker”, “antibiotic duration”, “antibiotic de-escalation” and “antimicrobial stewardship”. Searches were limited to human clinical studies without any restriction based on language.

3. Results

Since 2007, 4 prospective randomized studies evaluating the utility of PCT serums levels in reducing antibiotic duration have been published [55]-[58], of which all report beneficial outcomes (**Table 2**). All four studies utilized a similar design, in which a “PCT-directed intervention arm” was compared with a “standard of care arm”. The studies shared several common endpoints, specifically the reduction of antibiotic therapy duration (in days) and patient mortality, though each study utilized different criteria in determining the optimal timeframe for antibiotic discontinuation (**Table 3**). Nobre *et al.* [55] published the initial PCT level based intervention study involving 68 patients, and reported a 4-day reduction in antibiotic duration in the PCT arm ($p = 0.003$). Similarly, Hochreiter *et al.* [56] [57] demonstrated that patients in the PCT arm required 2 fewer days of antibiotics ($p < 0.001$) than the control arm, while Schroeder *et al.* found that the PCT intervention groups required 1.7 fewer days of antibiotics ($p < 0.001$). Finally, Bouadma *et al.* [58] performed the largest such study, involving 621 patients, and showed a 2.7-day reduction in antibiotics utilization ($p < 0.0001$) in the PCT arm. None of the 4 studies identified a significant difference in mortality between the PCT-directed intervention and control arms ($p > 0.05$) [55]-[58].

4. Discussion

Since the earliest documentation of antibiotic resistance in the 1940 s, several new drug classes have been established, with concomitant development of antibiotic resistance to many soon after their introduction [59] [60]. In past decades, medicine has witnessed a rise of new bacterial strains [61], including but not limited to MRSA (Methicillin-resistant *Staphylococcus aureus*), VISA (Vancomycin-intermediate *Staphylococcus aureus*), VRSA (Vancomycin-resistant *Staphylococcus aureus*), ESBL (Extended spectrum beta-lactamase), VRE (Vancomycin-resistant *Enterococcus*) and MDRAB (Multidrug-resistant bacteria acinetobacter baumanii). More recently

Table 2. Summary of all prospective randomized controlled trials evaluating Procalcitonin-guided antibiotic de-escalation in adult sepsis patients conducted between 2007 and 2013.

Study, Year	Total Patients (N)	PCT Arm			Control Arm			*p-value (Tx duration)	Outcomes
		Patients (N)	Tx duration (d)	Mortality†, N (%)	Patients (N)	Tx duration (d)	Mortality†, N (%)		
Nobre, 2007 [25]	68	31	6 (95% CI, 4 - 16) d	5 (16%)	37	10 (95% CI, 3 - 33) d	6 (16%)	$p = 0.003$	ABx duration decreased by 4 d in PCT arm
Hochreiter, 2009 [26]	110	57	5.9 ± 1.7 d	15 (26%)	53	7.9 ± 0.5 d	14 (26%)	$p < 0.001$	ABx duration decreased by 2 d in PCT arm
Schroeder, 2009 [27]	27	14	6.6 ± 1.1 d	3 (21%)	13	8.3 ± 0.7 d	3 (23%)	$p < 0.001$	ABx duration decreased by 1.7 d in PCT arm
Bouadma, 2010 [28]	621	307	14.3 ± 9.1 d w/o ABx	65 (21%)	314	11.6 ± 8.2 d w/o ABx	64 (20%)	$p < 0.0001$	ABx duration decreased by 2.7 d in PCT arm

Abbreviations: PCT = procalcitonin, N = number of patients, Tx = treatment, w/o = without, ABx = antibiotics, d = days, SD = standard deviation. †: 28-day mortality; *p-value: statistical significance, <0.05.

Table 3. Antibiotic discontinuation criteria for prospective randomized controlled trials relating to Procalcitonin-guided antibiotic de-escalation in adult sepsis patients conducted between 2007 and 2013.

Study, Year	Antibiotic Discontinuation Criteria
Nobre, 2007 [25]	ABx discontinued when PCT levels decreased by 90+% from initial value, but not prior to Day 3 (if baseline PCT measured <1 μg/L) or Day 5 (if baseline PCT measured ≥1 μg/L)
Hochreiter, 2009 [26]	ABx discontinued when PCT decreased to < 1 ng/mL, or to 25% - 35% of initial value over three days if value was >1 ng/mL
Schroeder, 2009 [27]	ABx discontinued when clinical signs of infection improved and PCT value decreased to <1 ng/mL or to <35% of initial value within three days
Bouadma, 2010 [28]	ABx discontinued when PCT concentration <80% of peak value, or absolute PCT concentration <0.5 μg/L

Abbreviations: PCT = procalcitonin, ABx = antibiotics.

MDR strains such as New Delhi metalloenzyme (NDM) beta lactamase carrying bacteria and Klebsiella pneumoniae carbapenemase (KPC) producing bacteria have emerged leaving patients on single antibiotic regimens susceptible to serious infections [62]. Studies by Scheetz *et al.* [13], Liew *et al.* [14] and others [12] [27] [28] have independently demonstrated that 22% to 65% of hospital antibiotic use is inappropriate, implying that the indiscriminate use and overuse of antibiotics is the single most important modifiable cause of antibiotic resistance.

For decades, antibiotic resistance was considered a pharmaceutical problem to be combated with the development of ever stronger antibiotics. However, given the numerous barriers to the development and utilization of new antimicrobial agents, including rising costs of research and development, tight drug approval and regulatory pathways, and uncertain rates of future drug resistance, the rate of new antibiotic discovery and implementation is unlikely to keep up with development of drug resistance [62]-[64]. Between 1983 and 2007, there has been a significant decrease in the number of new antibiotic approvals [65], having some experts comment that, "The research pipeline for novel antibiotics is almost dry" [64]. Thus, the most time-efficient and cost-effective approach to combat resistance is by optimizing the use of currently-available antibiotics [64].

Current recommendations for antibiotic duration of therapy for various infections are based largely on anecdotal guidelines put forth by the Infectious Diseases Society of America (IDSA) or the American Thoracic Society (ATS) [65] [66]. However, as RCT based evidence presented itself, the guidelines for antibiotic therapy continually changed. Data on safety and clinical efficacy made available from five RCTs and two meta-analyses lead to a five day reduction in the recommended treatment duration for CAP [40] [67]-[73]. Two of the five

RCTs were performed by Dunbar *et al.* [68] [69] from multiple US institutions comparing the efficacy of levofloxacin 750 mg for 5 days versus 500 mg for 10 days among 390 CAP patients and 149 atypical CAP patients with success rates >90% in all groups. Addtionally, in the multicenter RCT conducted among 575 patient with mild to moderate CAP by Tellier *et al.* [70], telithromycin 800 mg, 1 dose daily, for 5 and 7 days was found to be as effective and as safe as clarithromycin 500 mg, twice daily, for 10 days with cure rates of 89.3% at 5 days, 88.8% at 7 days, and 91.8% at 10 days. File *et al.* [71] analyzed 469 CAP patients treated with gemfloxacin 320 mg daily with equal clinical resolution in those treated for 5 days versus 7 days (95% versus 92%, 95% confidence interval: −1.48, 7.42). A more recent study by el Moussaoui *et al.* [74] found that even a three-day course of amoxicillin for treating CAP yielded similar clinical outcomes to an eight-day course of antibiotics. VAP was traditionally treated with a 14 to 21-day course of antibiotics until the report by Chastre *et al.* [40] [47] resulted in IDSA/ATS-recommended treatment duration guidelines being reduced by 7 days. With current literature promoting antibiotic de-escalation the utilization of serum biomarkers, such as procalcitonin may become the standard of care to improve outcomes, decrease costs, and decelerate antibiotic resistance [40] [66].

A growing literature on procalcitonin suggests significant potential for its use in the diagnosis of sepsis, although its role in clinical medicine continues to be controversial. Evaluations of serum PCT levels as a tool to predict disease severity and mortality has been met with mixed results [75]-[79]. Serum PCT level-based antibiotic escalation protocols were studied by Jensen *et al.* [80] [81] with results suggesting serum PCT levels have no well-defined clinical value in guiding antibiotic spectrum, dose or duration. Furthermore, PCT-guided therapy conferred no survival advantage and instead was associated with increased end-organ damage in this study.

In contrast, studies evaluating the use of serum PCT as a guide for de-escalation have demonstrated significant potential. Scheutz *et al.* [32] [82], Stolz *et al.* [83] and Luyt *et al.* [84] have all reported PCT-guided antibiotic discontinuation to be clinically efficacious when used in the context of lower respiratory tract infection (LRTI), specifically CAP [32] [82] and VAP [82]-[84]. Scheutz *et al.* [32] compared PCT-guided antibiotic algorithms to standard of care therapy for CAP and VAP patients and reported decreased antibiotic duration (5.7 versus. 8.7 days; relative change, −34.8%), with lower rates of antibiotic-associated adverse effects (19.8% vs. 28.1%) and comparable rates of adverse outcomes (15.4% versus. 18.9%). Stolz *et al.* [83] analyzed serum PCT level-based antibiotic discontinuation in VAP patients and reported a 27% reduction in overall antibiotic duration for the PCT study group. Finally, Luyt *et al.* [84] examined role of PCT serum levels for antibiotic discontinuation in VAP and ICU sepsis patients, concluding that despite its poor diagnostic value, serum PCT was useful as a prognostic marker and a guide for antibiotic discontinuation.

PCT-guided therapeutic interventions may provide a working solution to the ongoing issue of instituting stewardship practices, as the potential benefits of its use can lead to effective decreases in antibiotic duration and costs. However, there exist numerous barriers and limitations to ASPs and stewardship practices that must be overcome. One such obstacle is the determination of antibiotic spectrum and duration in patients undergoing empirical therapy for suspected infection. Several studies [29] [46] [85] have demonstrated that the prolonged use of antibiotics in cases of suspected infection does not necessarily provide any benefit, and may instead result in poor outcomes. Aarts *et al.* [85] established that empiric antimicrobial therapy continued for longer than 4 days in patients with suspected ICU-acquired nosocomial infection, resulted in increased 28-day mortality (32.1%) when compared to patients with discounted antibiotics (7.7%). Singh *et al.* [46] found that prolonged empiric treatment (>3 days) with broad-spectrum antibiotics in ICU patients with pulmonary infiltrates resulted in increased ICU length of stay (14.7 days vs. 9.4) and increased rates of antimicrobial resistance/superinfection (35%). Determining antibiotic spectrum and duration is a particularly important issue in the context of broad-spectrum antibiotic use in suspected or culture positive bloodstream infection [86], especially when considering the delay in culture and antibiotic sensitivity testing results [87].

An additional obstacle in implanting stewardship practices is physician attitude and obstinacy. In a review by Masterton *et al.* [30] antibiotic de-escalation rates ranged from 10% in clinical practice studies to 70% in trials focusing on de-escalation, suggesting that the persuasion of clinicians to utilize de-escalation protocols is a barrier in and of itself. The authors concluded that, “There is a natural propensity, particularly in severe sepsis when the patient who has been very seriously ill is starting to get better, to stick with a treatment regimen that is working rather than change to an alternative agent” [30]. This observation, paired with the difficulty of making prescribing decisions independently, often results in stewardship recommendations having a low-priority for many clinicians [88]. Wester *et al.* [89] conducted a survey on 424 internal medicine physicians’ attitude toward antibiotic use and reported that many are concerned about antimicrobial resistance in an inpatient setting, but

hold beliefs that are often at odds with established evidence-based data. 87% of respondents found antimicrobial resistance to be a serious national issue, but only 55% believed that the issue existed in their own hospitals [89]. Thus the study concluded that, "Many respondents see the risks as more theoretical than concrete, possibly weakening the impetus for behavior change" [89]. Though it may prove difficult to alter attitudes and perceptions rapidly, the primary solution appears to lie in the emphasis of education and behavioral modification.

Although APS may initially increase in overall cost of care and require additional manpower, stewardship practices are fiscally viable in both the long-term and short-term settings [90]-[93]. Beardsley *et al.* [93] studied on the financial impact of ASPs, and reported substantial savings as a result of reduced antibiotics expenditures amounting to approximately $920,070 to $2,064,441 per year. Moreover, Standiford *et al.* [91] reported financial benefits immediately following ASP implementation at one institution, noting a 37% decrease in antimicrobial costs within the first three years. As such, ASPs have clearly demonstrated a capacity to cut hospital expenditures with continued long-term fiscal viability.

5. Conclusion

In summary, PCT-guided early cessation of antibiotic therapy in adult sepsis patients is associated with a significant decrease in antibiotic days, without any change in overall mortality. Given the success of these trials, PCT may find a place in antimicrobial stewardship programs aimed at limiting antibiotic therapy duration while decelerating the development of antibiotic resistance. There still exist numerous barriers to the widespread establishment and implementation of antimicrobial stewardship programs, including delays in diagnostic procedure data, physician attitude towards de-escalation, and frontend institutional expenses. However, solutions to these problems are present or forthcoming, and will ultimately reinforce modern medicine's drive towards positive progress in antimicrobial practices.

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