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Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a US health system perspective

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Abstract

Background: Whether or not antibiotic stewardship protocols based on procalcitonin levels results in cost savings remains unclear. Herein, our objective was to assess the economic impact of adopting procalcitonin testing among patients with suspected acute respiratory tract infection (ARI) from the perspective of a typical US integrated delivery network (IDN) with a 1,000,000 member catchment area or enrollment.

Methods: To conduct an economic evaluation of procalcitonin testing versus usual care we built a cost-impact model based on patient-level meta-analysis data of randomized trials. The meta-analytic data was adapted to the US setting by applying the meta-analytic results to US lengths of stay, costs, and practice patterns. We estimated the annual ARI visit rate for the one million member cohort, by setting (inpatient, ICU, outpatient) and ARI diagnosis.

Results: In the inpatient setting, the costs of procalcitonin-guided compared to usual care for the one million member cohort was $2,083,545, compared to $2,780,322, resulting in net savings of nearly $700,000 to the IDN for 2014. In the ICU and outpatient settings, savings were $73,326 and $5,329,824, respectively, summing up to overall net savings of $6,099,927 for the cohort. Results were robust for all ARI diagnoses. For the whole US insured population, procalcitonin-guided care would result in $1.6 billion in savings annually.

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Conclusions: Our results show substantial savings associated with procalcitonin protocols of ARI across common US treatment settings mainly by direct reduction in unnecessary antibiotic utilization. These results are robust to changes in key parameters, and the savings can be achieved without any negative impact on treatment outcomes.

Keywords: antibiotic stewardship; cost saving; economic evaluation; procalcitonin; respiratory infection.

Introduction

Improved diagnostics and clinical biomarkers have been shown to be an important part of cost-effective medical care in acute care settings [1–8]. Biomarkers have shown to be very effective in aiding diagnosis and management of hospital patients with suspected systemic bacterial infections, including community-acquired pneumonia (CAP) and sepsis [9–28]. Procalcitonin (PCT) is a novel and effective marker of assumed bacterial infections that safely helps guide antibiotic therapy in acute respiratory tract infections (ARI) and sepsis in hospitals [5, 29–40].

The use of PCT supplies caregivers with added information, which, in principle, enables them to improve the selection of patients for treatment, the timing of treatment initiation, and the overall duration of treatment [21, 28, 32, 33, 35, 41–47]. Insofar as caregivers change their care management and treatment strategies in response to the new information (relative to the usual standard course of action), there are implications for changes in outcomes, both in terms of treatment costs and health status [14, 33, 35].

There is strong evidence that PCT-guided care management results in reductions in antibiotic exposure and possibly costs [33, 35, 37, 38, 48–53]. For example, a comparative effectiveness summary report from the US Agency for Healthcare Research and Quality ("AHRQ"; 2012) concluded that there was high strength of evidence in support of PCT reducing antibiotic usage, with relative reductions ranging from 21% to 38% [53]. According to the AHRQ report, some studies have shown differences in hospital intensive care unit (ICU) length of stay (LOS) and overall hospital LOS between usual care and PCT-guided care [48]. In most studies, the PCT-guided arm of the study was associated with LOS reductions between 0 and 2.5 days (0%–11%) [53]. Many of these studies did not show statistically significant results, although the one study with significant results found a 43% reduction in ICU LOS associated with PCT testing.

Recently, Schuetz et al. (2012) performed a meta-analysis of patient-level data from 4221 adults with ARIs from 14 clinical trials [33]. In addition to a marked reduction in antibiotic exposure, they found significant differences in treatment failure (defined as "death, hospitalization, ARI-specific complications, recurrent or worsening infection, and discomfort at 30 days") overall between the PCT group and the control group (19.1% and 21.9%, respectively). Among sub-groups, these differences were also observed in the emergency department (ED) and for patients with CAP. A meta-analysis of five studies found that PCT-guided treatment results in a 0.4 percentage point reduction in mortality [53].

Economic evaluations have shown that the clinical advantages associated with PCT-guided care also result in net savings of healthcare resources. PCT has the potential to improve the management of health care resources a number of ways, including: 1) reducing unnecessary antibiotic prescriptions and supporting improved antibiotic stewardship; 2) reducing hospital LOS; 3) improving the timing of diagnosis and treatment; and 4) improving the ability of clinicians to optimally match diagnosis and treatment [5, 34, 51, 54–60].

Based on published randomized trials of PCT-guided treatment in Canadian hospital intensive care units, Heyland et al. conducted a cost-minimization analysis based on the costs of PCT testing and antibiotic acquisition and administration [51]. PCT-guided strategies were associated with a significant reduction in antibiotic use, and PCT-guided care was not associated with any differences in hospital mortality. Michaelidis et al. assessed the cost-effectiveness of PCT-guided antibiotic therapy (vs. usual care) in outpatient management of ARI in adults, based on the results of two published European clinical trials [56]. In the cohort including all adult ARIs judged to require antibiotics by their physicians, the costs of PCT-guided care was $31 per antibiotic prescription safely avoided and the likelihood of PCT use being favored (compared to usual care) was 58.4% in a probabilistic sensitivity analysis – an amount well below the willingness-to-pay. PCT-guided care also appears to have cost-saving effects in sepsis care. Deliberato et al. assessed patients with suspected sepsis, severe sepsis, or septic shock in a hospital ICU, and found that in the PCT-guided group median antibiotic duration was 9 days vs. 13 days in the non-PCT group [50].

The existing economic literature on PCT has several important gaps. First, none of the existing studies examine the cumulative economic effects of PCT in all of the clinical settings in which it can be employed (i.e., hospital wards, hospital ICUs, and outpatient clinics and EDs). Second, the existing economic studies do not make

full use of recent meta-analyses of clinical trials, such as Schuetz et al. [33, 34]. Third, none of the economic studies pertain to the US market. Our study fills these three gaps in the current PCT economic literature by examining effects across all the different clinical settings in which PCT may be used, making use of recent meta-analytic studies of PCT clinical effectiveness, and focusing on the US health system, including US cost structure and practice patterns.

The objective of this study is to assess the clinical and economic impact of adopting PCT testing and monitoring versus usual care among patients with suspected lower respiratory tract infection from the perspective of a typical US integrated delivery network (IDN) or payer with a 1,000,000 member catchment area or enrollment. Our study fills the aforementioned gaps in the current PCT economic literature by examining effects across all the different clinical settings in which PCT may be used, making use of recent meta-analytic studies of PCT clinical effectiveness, and focusing on the US health system.

Materials and methods

For this analysis we used patient-level data from a recently published comprehensive meta-analysis of available clinical trial data [33]. The protocol for this meta-analysis is published in the Cochrane Library [61]. In brief, 4221 patients with different types of respiratory infections of varying severity, including upper respiratory infections, acute bronchitis (AB), exacerbation of chronic obstructive pulmonary disease (ECOPD), CAP and ventilator-associated pneumonia (VAP) from 14 randomized trials were included in this analysis. The main variables used from the meta-analytic database were days of antibiotic exposure by diagnosis and setting.

To conduct the economic evaluation of PCT testing and monitoring versus usual care we built a cost-impact model in MS Excel®. The patient population in this study is patients with suspected ARI infection diagnoses seen in one of three settings: inpatient hospital setting (not in the ICU); hospital ICU; outpatient clinic or ED based on the meta-analysis data. We first estimated the annual ARI visit rate per 100,000 population, by setting and diagnosis (Table 1). The numerator (number of visits) is based on recent US national inpatient and outpatient population surveys [63, 64]. Rates were then calculated based on population estimates from the US Census. The expected number of annual visits was then estimated by multiplying plan size by the estimated rate (Table 1).

We modeled PCT testing differently for each treatment setting. For inpatient stays we assumed that there would be an initial PCT test upon initial presentation (e.g., ED admitted to ward or ICU) and subsequent monitoring tests every other day until discharge. For partial days we rounded to the nearest whole day of stay (i.e., 5.2 LOS – tests on Days 1, 3 and 5). Outpatient care (e.g., ED discharged home, hospital outpatient or office visit) assumed a single PCT test to support antibiotic initiation.

Cohort patients are assumed to enter the "usual care" arm or the PCT arm. To model the effect of routine PCT utilization we compare the same number of patients in each treatment protocol. The treatment algorithm is adapted to setting of care as described above. For example, we assume no PCT follow-up monitoring in the outpatient setting. Based on the clinical studies included in the meta-analytic data, the costs and outcomes of each ARI episode is assessed over a 30-day period. Total costs and events are annualized based on the incidence of each condition and likelihood of treatment success and intensity. Depending on which arm of the decision tree a patient travels, the costs of antibiotic therapy and monitoring, PCT testing, total number of patients on antibiotic therapy, and total days of antibiotic

Table 1 Acute lower respiratory infection rates and estimated number of annual cases in a typical US integrated health system and patient-level mean antibiotic initiation, by treatment protocol, setting and diagnosis.

Setting/ diagnosis	No. of annual cases per 1 million insured[a]	Mean antibiotic initiation rate[b]		
		PCT	Usual care	% Point difference PCT vs. UC[c]
Hospital Ward/ED	5006	75.7% (0.43)	89.5% (0.31)	−15.5
AB	350	29.4% (0.46)	65.3% (0.48)	−55.0
CAP[d]	2960	93.0% (0.26)	99.7% (0.06)	−6.7
ECOPD	1697	50.0% (0.50)	74.1% (0.44)	−32.5
Hospital ICU	528	99.7% (0.06)	100.0%	−0.3
CAP[e]	522	100.0%	100.0%	0.0
VAP/HAP[f]	5	99.4% (0.08)	100.0%	−0.6
Clinic/ED	53,651	36.2% (0.48)	69.3% (0.46)	−47.8
AB	22,378	22.7% (0.42)	65.7% (0.48)	−65.5
CAP	14,999	75.4% (0.43)	97.0% (0.17)	−22.2
ECOPD	16,275	36.5% (0.49)	67.9% (0.47)	−46.2

See text. [a]Based on data from the US Census [62], US HCUP [63] and US NAMCS-NHAMCS [64], per 1,000,000 insured lives in a US integrated delivery system; [b]Standard deviations in brackets; [c]percentage point difference; [d]assumes 85% of all CAP discharges are treated in hospital ward; 100% of COPD and AB cases treated in ward; [e]assumes 15% of all CAP discharges are admitted to ICU; [f]100% of VAP/HAP admitted to hospital ICU. AB, acute bronchitis; CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; UC, usual care; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

exposure are summed. Differences in antibiotic initiation rates, antibiotic therapy days among those initiated on antibiotic therapy and percent successfully treated are based on the Schuetz et al. meta-analysis [33] (Tables 1 and 2).

Baseline US hospitalization LOS and overall costs of care for selected ARI inpatient care are shown in Table 3, based on an analysis of the US Health Care Cost and Utilization Project (HCUP) National Inpatient Sample [63]. The table also shows weighted mean costs per episode for these diagnoses; these data are provided as background and not used in subsequent analyses. In the model, we assumed that the mean baseline number of antibiotic days corresponds to the average LOS for a typical hospitalization (Table 3).

The perspective of the model is that of a US IDN or payer assuming full or partial financial risk for all sites of care. We therefore developed the cost-impact model to capture the current burden of managing suspected ARI and the potential impact of implementing routine PCT testing. The model describes the expected annual rate of visits, site of service and diagnosis mix across the plans catchment area or enrolled population. The cohort enters the model at risk for an ARI episode and may present for care at one of three sites of service described earlier. The likelihood of presentation at each site and with each diagnosis is based on US annual incidence rates [63, 64].

The primary outcome measure was total antibiotic-related costs by setting (hospital ward/ED, hospital ICU, or clinic/ED) attributable to PCT-guided care versus usual care. Daily costs of antibiotic therapy for inpatient stays were estimated based on typical daily dosage multiplied by the wholesale acquisition cost of each drug. Typical dosages and mix of expected therapy were derived from published clinical treatment guidelines [65–75]. Guidelines outline multiple treatment options and patients may require more than one antibiotic administered concurrently. In these cases we estimated the weighted average cost of a prototypical representative of a given drug class weighted by the likelihood of receiving multiple drugs during a typical stay (Table 4). Daily cost of antibiotic administration was estimated based on a recently published cost analysis [76].

The cost of PCT testing (HCPCS 84145) was estimated based on the average Medicare laboratory payment in 2014. Physician time associated with interpreting the PCT test was not included in the model because the associated costs have been found to be negligible [56]. Outpatient clinic treatment costs were estimated based on a recent study that examined the economic impact of antibiotic utilization incorporating estimates of the cost of initial antibiotic therapy but also induced follow-on costs associated with a new antibiotic prescription [56]. Costs are expressed per episode and were converted to per day costs using a typical average length of antibiotic therapy.

Daily costs attributable to antibiotic resistance were derived from a recent economic study of antibiotic use in the clinic setting [56]. This analysis used recent US national estimates of excess cost attributed to resistance and derived antibiotic cost per prescription

Table 3 National average length of stay and inpatient costs among ARI patients in the US, 2014.

Condition/ disease	ICD9 code ranges	Mean length of hospital stay (2011)[a]	Mean total hospital costs per episode (2014)[b]	Mean total hospital costs per day (2014)[c]
AB	466.0, 466.19	3.0	$5086	$1695
CAP	485, 486, 481,482, 483	5.1	$9925	$1946
ECOPD	491.21–491.21	4.4	$8202	$1864
HAP/VAP	997.31	13.0	$34,481	$2652
Mean[d]		5.9	$12,790	$2067

[a]Based on calculations using the 2011 public-use inpatient sample data from HCUP; [b]Based on 2011 HCUP calculations, trended forward to 2014 using the consumer price index inflation adjuster; [c]Total hospital costs per episode divided by mean length of stay per episode; [d]Weighted by case volume. AB, acute bronchitis; CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

Table 2 Patient-level mean antibiotic days among those initiated on antibiotic treatment, and percent successfully treated: by treatment protocol, setting and diagnosis.

Setting/ diagnosis	Mean antibiotic days[a]			Successfully treated patients[a]		
	PCT	Usual care	Percent difference PCT vs. UC[b]	PCT	Usual care	Percent difference PCT vs. UC[a]
Hospital Ward/ED	7.76 (5.02)	10.73 (5.58)	−27.7%	82.8% (0.38)	83.3% (0.37)	−0.6
AB	4.50 (3.68)	7.10 (3.86)	−36.6%	82.4% (0.38)	84.0% (0.37)	−2.0
CAP	8.10 (5.09)	11.61 (5.47)	−30.3%	80.8% (0.39)	81.7% (0.39)	−1.1
ECOPD	6.81 (4.29)	8.33 (3.68)	−18.2%	87.3% (0.33)	87.2% (0.33)	0.1
ICU	10.52 (6.86)	13.73 (7.27)	−23.4%	80.1% (0.40)	76.2% (0.43)	5.2
CAP	9.01 (5.65)	13.44 (7.49)	−33.0%	62.3% (0.49)	57.8% (0.50)	7.8
VAP/HAP	11.78 (7.51)	14.00 (7.07)	−15.8%	94.9% (0.22)	92.7% (0.26)	2.4
Clinic/ED	6.27 (3.18)	7.86 (3.32)	−20.2%	75.1% (0.43)	75.4% (0.43)	−0.5
AB	7.66 (3.02)	7.19 (2.63)	6.5%	72.9% (0.45)	75.8% (0.43)	−3.8
CAP	5.99 (3.34)	8.52 (3.95)	−29.6%	85.1% (0.36)	87.0% (0.34)	−2.1
ECOPD	5.16 (2.24)	8.83 (3.56)	−41.6%	82.7% (0.38)	79.2% (0.41)	4.3

See text. [a]Standard deviations in brackets; [b]Percent difference. AB, acute bronchitis; CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; UC, usual care; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

Table 4 Cost parameters by setting and diagnosis.

Diagnosis/setting/measure	Value
Hospital ward/ED	
Antibiotic cost, per day	
Acute bronchitis	$25.13
CAP	$73.18
ECOPD	$49.07
Hospital ICU	
Antibiotic cost, per day	
CAP	$73.18
HAP/VAP	$362.22
Antibiotic administration cost, per day[a]	$59.39
Clinic/ED[b]	
Initial antibiotic prescription cost, per day	
AB	$9.10
CAP	$16.35
ECOPD	$9.10
Follow-up costs, per day	
AB	$14.67
CAP	$32.53
ECOPD	$14.67
PCT Cost per test[c]	$49.38

See text. [a]Based on Van Zanten et al. [76]; [b]Per episode costs, including induced follow-on costs such as office visits (based on Monte et al. [77]; [c]CMS HCPCS 84145 – National Medicare Midpoint 2014. AB, acute bronchitis; CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

and allocated costs based on the volume of antibiotic prescriptions annually for ARI in the US. The estimated cost per prescription was $43. We estimated the daily costs of antibiotic resistance by dividing the cost per prescription by the average duration (number of days) of a typical antibiotic prescription.

We conducted one-way deterministic sensitivity analyses on selected measures, including: 1) percentage reduction in antibiotic days in the PCT group; 2) daily cost of antibiotics and monitoring; 3) type of PCT protocol followed in hospital settings; and 4) antibiotic resistance costs.

Results

Overall results

Results of the cost impact model by clinical setting are shown in Table 5. In all three settings, PCT-guided care was shown to be cost saving across all treatment settings and diagnoses. In the hospital ward and ED, the costs of PCT-guided care for the one million member cohort was $2,083,545, compared to $2,780,332 for the usual care group, resulting in net savings of nearly $700,000 to the IDN. The ICU setting also resulted in savings ($73,326), but the savings were smaller than other settings because US protocols heavily favor empirical prescribing of antibiotics in hospital ICUs [73].

The outpatient clinic and ED are where PCT has its largest effect. In the clinic and ED, the costs of PCT-guided care for the cohort was $5,624,532, compared to $10,954,356, resulting in net savings of $5,329,824 to the IDN. Across all three settings, PCT-guided care is associated with a total cost of $8,033,338 for the one million member cohort, compared to $14,133,265 for the usual care group, resulting in an overall net savings to the IDN of $6,099,927.

Sensitivity analysis

To test the impact of model assumptions we conducted a series of one-way deterministic sensitivity analyses. Key model parameters were increased or decreased by 20% to assess the effect of each assumption on model results. The key output measure was the total cost difference across all three clinical settings (–$6,099,927). We conducted analyses on the following model inputs: 1) percentage reduction in antibiotic days in the PCT group; 2) daily cost of antibiotics and monitoring; 3) type of PCT protocol (i.e., frequency of testing) followed in hospital settings; and 4) antibiotic resistance costs.

Model results are most sensitive to estimates of the daily cost of antibiotic treatment, ranging from $4.8 million savings to $7.4 million savings. Percentage reduction in antibiotic days in the PCT group is the next most important factor, with savings ranging from $5.6 million at the lower bound to $6.7 million at the upper bound of the range (Figure 1). The costs of antibiotic resistance had only a modest impact on the results, ranging from $5.8 million to $6.3 million at the lower and upper bounds, respectively. PCT test frequency among hospitalized patients had the smallest impact, ranging from $5.7 million in savings if the test is administered once a day versus $6.1 million in the base case protocol where testing was assumed to occur every other day (Figure 1).

We also tested the sensitivity of the model with respect to baseline antibiotic initiation rates. For this analysis we focused on CAP, because in the US the vast majority of CAP patients are started on antibiotics in all three settings (see Table 5). However, the sensitivity analysis showed that PCT-guided care resulted in savings even with CAP antibiotic initiation rates as low as 65%, holding all other variables constant.

Table 5 IDN budget impact of PCT versus usual care in treatment of ARI in US hospitals, by setting, 2014.

Protocol/diagnosis	N[a]	Initiated on ABx[b]	Reduction days ABx	PCT Testing Cost[c]	Number of ABx days	Daily ABx costs	ABx resistance cost	Total cost of ABx
Hospital ward/emergency department[d]								
PCT								
AB	350	29.4%	−36.6%	$5077	195	$85	$1173	$22,769
CAP	2960	93.0%	−30.3%	$271,797	9783	$133	$58,698	$1,627,391
ECOPD	1697	50.0%	−18.2%	$83,793	3054	$108	$18,326	$433,385
Total	5006				13,033		$78,197	$2,083,545
Usual care								
AB	350	65.3%	NA	$0	685	$85	$4111	$62,023
CAP	2960	99.7%	NA	$0	15,049	$133	$90,294	$2,085,285
ECOPD	1697	74.1%	NA	$0	5531	$108	$33,184	$633,013
Total	5006				21,265		$127,589	$2,780,322
PCT Value to IDN (Hospital/ED)					−8232		−$49,392	−$696,777
Hospital ICU[d]								
PCT								
CAP	522	100.0%	−33.0%	$51,586	1786	$133	$10,716	$299,064
VAP/HAP	5	99.4%	−15.8%	$1560	58	$422	$346	$26,197
Total	528				1844		$11,062	$325,261
Usual care								
CAP	522	100.0%	NA	$0	2664	$133	$15,983	$369,126
VAP/HAP	5	100.0%	NA	$0	69	$422	$413	$29,462
Total	528				2733		$16,397	$398,588
PCT value to IDN (Hospital ICU)					−889		−$5335	−$73,326
Clinic/ED								
PCT								
AB	22,378	22.7%	6.5%	$250,312	37,790	$24	$226,739	$1,375,260
CAP	14,999	75.4%	−29.6%	$558,725	55,751	$49	$334,508	$3,618,678
ECOPD	16,275	22.7%	−41.6%	$182,039	15,068	$24	$90,409	$630,595
Total	53,651				108,609		$651,655	$5,624,532
Usual care								
AB	22,378	65.7%	NA	$0	102,918	$24	$617,509	$3,063,725
CAP	14,999	97.0%	NA	$0	101,796	$49	$610,773	$5,587,120
ECOPD	16,275	67.9%	NA	$0	77,381	$24	$464,284	$2,303,511
Total	53,651				282,094		$1,692,566	$10,954,356
PCT value to IDN (Clinic/ED)					−173,485		−$1,040,910	−$5,329,824
Total PCT value to IDN					−182,606		−$1,095,637	−$6,099,927

See text & Table 1. [a]See Table 1; cohorts based on 1,000,000 covered lives in a US integrated delivery system; [b]Based on Schuetz et al. [33, 34]; [c]See Table 4; assumes one test on the first day of admission and follow-up tests every other day while in hospital in the PCT cohort; [d]includes $59 per day antibiotic administration costs (see Table 4). AB, acute bronchitis; ABx, antibiotics; CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

As the model was most sensitive to the daily costs of antibiotics, we also conducted a break-even analysis. For this analysis we considered only the direct cost impact comparing cost of PCT testing to cost savings associated with reduced antibiotic use. Our analysis suggests that PCT testing would maintain cost savings even when antibiotic treatment costs are assumed to be only 22% of our base model assumption. Put differently, this suggests that daily antibiotic costs could be nearly one-fifth of our assumed value for a strategy of PCT testing to remain at least cost neutral to a typical US IDN.

Discussion

Our results show substantial savings associated with the use of PCT to guide antibiotic treatment of ARI across common US treatment settings. Across all three settings, PCT-guided care is associated with a total of $5,887,535, compared to $12,296,714 for usual care, resulting in an overall net savings to the IDN of $6,099,927 based on a population of 1,000,000 insured lives. These results are robust to changes in key parameters. In the sensitivity analysis, most parameter variations resulted in only

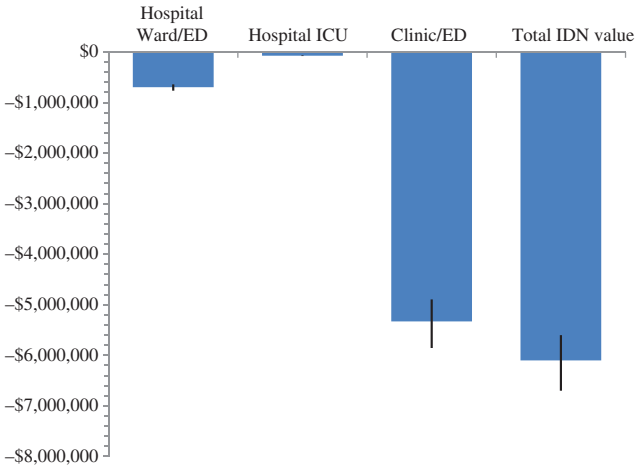

Figure 1 IDN budget impact and confidence intervals based on days of antibiotic exposure: PCT versus usual care in treatment of ARI in US hospitals, by setting, 2014.

small changes in total savings. The results were sensitive to daily antibiotic treatment costs, which are likely to vary to some degree regionally and among different IDNs, but the ±20% variation still results in savings of at least $5 million to the IDN.

These results are similar to those of Heyland et al. and Michaelidis et al., both of which found substantial savings attributable to PCT-guided treatment protocols [51, 56]. Interesting, those studies reached similar conclusions but relied on methods substantially different than ours. This adds to the robustness of the results.

We modeled the cost differential that would be realized within a US IDN with 1,000,000 covered lives. In the US, there are 262,246,800 individuals with some form of health insurance. Extrapolating to this larger population, based on our model PCT-guided care would result in approximately $1.6 billion in savings nationally. If we assume that, to some extent, the recently passed Affordable Care Act (ACA) in the US will extend insurance to the entire population, the total savings attributable to PCT-guided care would be about $1.9 billion nationally.

It is important to emphasize that the savings associated with PCT-guided care is not associated with any meaningful differences in quality, which has been a consistent finding of clinical effectiveness studies of PCT to date [5, 30, 34, 38, 52, 78, 79]. Moreover, our calculations take into account the costs of the tests and the administration of the tests. The implication is that the savings are "real" savings to an IDN – the tests more than pay for themselves without negatively affecting treatment outcomes. In addition, it is important to stress that our estimate of the daily costs of antibiotic resistance is likely very conservative, as increasingly the literature and reports on antibiotic resistance suggests that the amount might be substantially higher [80].

Previous studies have not directly assessed differences in outcomes in quality of life and functioning dimensions following PCT-guided treatment [53]. However, given that time spent in-hospital generally is associated with a lower level of health-related quality of life (HRQoL) than time spent out of hospital, PCT-guided treatment would be likely to translate into improvements in HRQoL if it reduces hospital LOS. Similarly, adverse effects of antibiotic treatment may reduce HRQoL; thus the reduction in antibiotic exposure resulting from PCT-guided treatment also may translate into improvements in HRQoL.

A key assumption is whether PCT testing correlates with actual change in care management; that is, to what extent do physicians react to the results of PCT testing? Put differently, to what extent do physicians weigh PCT results versus other forms of clinical information? In economic models of diagnostics, a common challenge is determining whether the existence of new or different information actually changes physician behavior. In a randomized study design, where patients are randomized to PCT-guided care versus usual care, this problem may not be too serious because, in theory, any differences in endpoints can be attributed to the intervention. However, the extent of this causal relationship is dependent on the overall quality of the study design. Moreover, any given hospital could argue that their physicians and care management teams "tend to do things differently." For example, Dusemund et al. found considerable variation in how physicians react to PCT test results [35].

Another potential limitation of our study is that the meta-analytic data used pertain primarily to European settings. The model was designed to account for these differences in two ways – by using US data on LOS, utilization rates, and costs, and by applying US practice patterns as reflected in clinical practice guidelines. Although this approach is likely to provide a reasonable approximation of the cost impact of PCT in US clinical settings, a more definitive approach would have been to use US trial data analogous to the meta-analytic data compiled by Schuetz et al. Such data, however, were not available for this study.

Conclusions

Our results show substantial savings associated with the use of PCT to guide antibiotic treatment of ARI in common US treatment settings. Across all three settings,

PCT-guided care is associated with net savings ranging from $73,326 in the ICU to >$5 million in the outpatient clinic and ED setting, for total savings to the IDN of more than $6 million. These results are robust to changes in key parameters, and the savings can be achieved without any negative impact on treatment outcomes.

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