Procalcitonin concentrations in bacteremia

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Summary

Background. Distinguishing sepsis from other non-infectious conditions in critical patients with clinical signs of acute inflammation is challenging. Procalcitonin (PCT) has recently been now acknowledged as one of the most useful laboratory parameters for increasing the accuracy of diagnosing sepsis, for monitoring patients at high risk, for prognostic assessment and therapeutic control, but little information is available on its relationship with blood culture test and C reactive protein (CRP). Therefore, the aim of this study was to compare PCT with CRP and blood culture from a laboratory standpoint.

Methods. A total of 1358 samples referred for PCT testing were considered. All the samples were from patients hospitalised at the Rovereto Hospital and other facilities pertaining to Trento Provincial Health Service (APSS). PCT was measured using EDTA plasma specimens on the automatic analyser KRYPTOR, whereas CRP was measured by an Olympus latex-amplified immunoturbidimetric assay. Bactec 9240 was used to detect bacterial growth in the blood samples. A total of 798 samples for measurement of CRP were also processed, along with 1529 blood culture specimens.

*Results.*1343 (88%) out of the 1529 blood culture performed were negative and 186 (12%) were positive. 861 (63%) tests yelded to a PCT level below the detection limit of the assay (0.5 ng/ml). Of these 798 C-reactive protein tests, 728 were significant, above 6 mg/l, and just 70 were not significant.

In our study, the highest value of PCT observed was 352 ng/mL, associated with four positive blood culture vials where *Escherichia coli* was isolated. The microorganisms most frequently isolated were: *Staphylococcus epidermidis* 20, *Escherichia coli* 16, *Staphylococcus aureus* 8, *Staphylococcus hominis* 6, *Streptococcus pneumoniae* 4, *Klebsiella pneumoniae* 3, *Pseudomonas aeruginosa* 3.

The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with low PCT values (<2 ng/mL): *Staphylococcus epidermidis* 16, *Staphylococcus hominis* 4, *Staphylococcus aureus* 3, *Escherichia coli* 3, *Corynebacterium spp.*. The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with intermediate PCT values (from ≥ 2 to <10 ng/mL): *Escherichia coli* 4, *Staphylococcus epidermidis* 2, *Staphylococcus aureus* 2, *Streptococcus pneumoniae* 2, *Haemophilus influenzae* 2. The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with high PCT values (≥ 10 ng/mL): *Escherichia coli* 9, *Staphylococcus aureus* 3, *Staphylococcus epidermidis* 2, *Staphylococcus hominis* 2, *Streptococcus pneumoniae* 2, *Pseudomonas aeruginosa* 2.

Conclusions. Although we found a strong correlation between positive blood culture tests and high PCT values, some positive blood cultures have near to normal levels. Overall, gram-positive blood culture tests were clearly associated with the PCT levels moderately higher than the diagnostic threshold, whereas gram-negative blood cultures were associated with considerably higher. We also found a good agreement between negative blood cultures and PCT values, either lower than the diagnostic cutoff or comprised between 2.0 and 10.0 ng/mL, allowing us to conclude that PCT has a high negative predictive value. Procalcitonin is far more specific and reliable than C-reactive protein as regards systemic inflammation. Unlike procalcitonin, PCR increases greatly in localised inflammation, but does not reflect inflammatory condition patterns equally well.

Taken together, our results confirm that measurement of PCT would be suitable to provide important indications for the therapeutic control of infection, contributing to a potential reduction in antibiotic treatment.

Key-words: Sepsis, PCT, CRP, bacteremia.

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Introduction

Distinguishing sepsis from other non-infectious conditions in critical patients with clinical signs of acute inflammation is challenging. This is instead an important issue, since early diagnosis and prompt instauration of specific therapies are both associated with an improved outcome of patients with sepsis[1,2]. The most frequently inflammatory parameters [body temperature, leukocytosis, increased C-reactive protein (CRP) levels] have often poor sensitivity and specificity and are therefore of limited help in the management of these patients[3]. On the other hand, bacterial culture, which is the gold standard for diagnosing infection, has some drawbacks, including a long turnaround time, it does not provide specific information on host response and it is unable to distinguish between bacterial colonisation and systemic complications such as systemic inflammatory response to infection or invasive bacterial infection. Procalcitonin (PCT), the precursor of calcitonin normally synthesized in the C-cells of the thyroid gland, is now acknowledged as one of the most useful laboratory parameters for increasing the accuracy of diagnosing sepsis, for monitoring patients at high risk, for prognostic assessment and therapeutic control[4].

The aim of this study is to compare PCT with C-reactive protein and blood culture from a laboratory standpoint. Specifically, the Authors attempt to find a correlation between PCT levels and the results of microbiological assay for blood culture.

Materials and Methods

A total of 1358 samples referred for PCT testing were considered. A total of 798 samples for measurement of CRP were also processed, along with 1529 blood culture specimens. All the samples were from patients hospitalised at the Rovereto Hospital and other facilities pertaining to Trento Provincial Health Service (APSS).

From October 2006 to June 2007, CRP and PCT levels were daily recorded, along with results of blood culture tests on the same patients. During this period, the Rovereto Clinical Chemistry and Microbiology Test Laboratory processed 1358 samples PCT was measured using EDTA plasma specimens on the automatic analyser KRYPTOR (Brahms Gmbh, Berlin, Germany). This method uses TRACE (time-resolved amplified cryptate emission) technology, based on the non-radioactive energy transfer between two fluorescent tracers: europium cryptate (the donor) and XL665 (acceptor). The PCT molecules in the blood sample are sandwiched between the antibodies and signal intensity is proportionate to the concentration of PCT. Analitical sensibility was 0.02 ng/mL and inter-assay CV was 3%.

The Olympus System reagent CRP assay (Olympus Italia S.R.L., Segrate, Milan, Italy) is based on a latex-amplified immunoturbidimetric reaction. The goat antibody used is obtained after immunisation with human CRP. When a sample containing CRP is mixed with the buffer solution and latex solution, human CRP reacts in a specific manner with anti-CRP antibodies, to produce insoluble aggregates. These aggregates formed in the solutions, deviate light in proportion to their size, shape and concentration. The procedure of application on Olympus analyzers, the decrease in the intensity of the light transmitted (increase in absorbance), is the result of the immunological complex that forms during the antigen-antibody reaction. The increase in absorbance detected photometrically is directly proportionate to the concentration of CRP in the sample.

Bactec 9240 (Becton, Dickinson and Conpany, Buccinasco, Milan, Italy) is an automatic system for continuous detection of bacterial growth in the blood and biological liquids. The system controls, stirs and incubates at 35°C up to 240 vials at any one time. Each vial contains a chemical sensor that can detect the increase in CO_2 produced by microorganism growth. Every 10 minutes, the instrument checks sensor fluorescence, which is directly proportionate to the increase in CO_2 present. The bacterial growth in the liquid phase is detected by means of a fluorimetric method. The sensor on the bottom of the vial contains fluorescent compounds that react in the presence of CO_2. The data has been collected and processed using a Microsoft Excel spreadsheet and the variables of the sample studied (number of determinations, age, sex, submitting department) are expressed as an absolute frequency and percentage.

Results

Out of the total 1358 samples referred for PCT testing, 726 (53 %) were from female patients and 632 (47%) from males. The age of tested patients was clustered within four classes: elderly (>65 y), adult (14 – 65 y), paediatric (1 – 14 y) and newborn (< 1 y).

774 out of 1358 samples (58%) were from elderly patients, 372 (27%) from adults, 124 (9%) from children and the remaining 88 (6%) from newborns.

The wards and/or units requesting PCT testing were in decreasing order: Internal Medicine (628, 47%), Paediatrics (216, 17%), Geriatrics (114, 9%) and the Intensive Care Unit (ICU) (104, 8%).

861 (63%) tests yielded to a PCT level below the normal range of the assay (0.5 ng/ml).

When analyzing results of PCT testing according to their origin, test results with PCT values ≥ 0.5 ng/ml were 98 (19%) in Geriatrics, 76 (15%) in the Intensive Care Unit (ICU), 191 (39%) in Internal Medicine, 86 (17%) in Paediatrics and 52 (10%) in the remaining wards of the hospital.

54 (6%) out of the 857 patients who had PCT requested underwent an average of 5.4 serial measure-

ments, with a minimum of 4 and a maximum of 11 tests.

A total of 798 samples for measurement of CRP were also processed, along with 1529 blood culture specimens.

1343 (88%) out of the 1529 blood culture performed were negative and 186 (12%) were positive (Table I). Specifically, 22 vials were processed from newborns, all of which were negative and showed PCT values within the normal range, with the exception of one case (29 ng/mL). Among the children, 62 blood culture vials were processed, and 1 was positive for *Staphylococcus epidermidis*. This patient displayed PCT levels of 1.04 ng/mL and CRP of 138 mg/L. In the adult age class, 497 vials were considered, 63 of which were positive. In the elderly bracket, 948 vials were considered, 120 of which were positive.

In our study, the highest value of PCT observed was 352 ng/mL, associated with four positive blood culture vials where *Escherichia coli* was isolated.

The microorganisms most frequently isolated were: *Staphylococcus epidermidis* 20, *Escherichia coli* 16, *Staphylococcus aureus* 8, *Staphylococcus hominis* 6, *Streptococcus pneumoniae* 4, *Klebsiella pneumoniae* 3, *Pseudomonas aeruginosa* 3 (Table II).

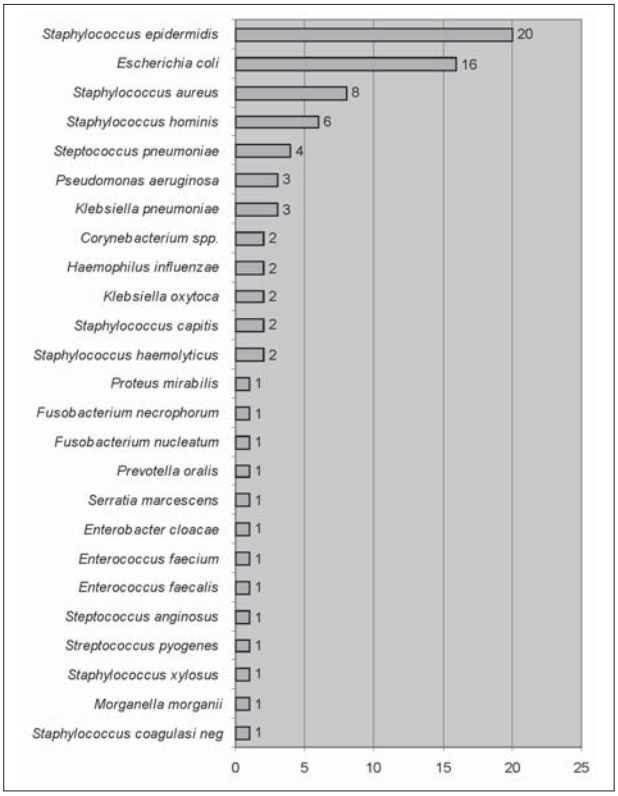
The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with low PCT values (<2 ng/mL): *Staphylococcus epidermidis*

Table I. Microorganisms identified in 186 positive blood cultures of n° 78 patients (sex, department and age) and PCT and PCR values, respectively.

Paz n°	*Sex*	*Department*	*Age*	*PCT*	*PCR*	*blood culture vials*	*bacterial growth (microorganisms)*
1	F	MED	89	0,12	4,2	2 neg, 2 pos	*Staphylococcus hominis*
2	M	PED	1	1,04	138,9	1 positive	*Staphylococcus epidermidis*
3	F	MED	56	76,01	286,9	3 positive	*Escherichia coli*
4	M	CHIR	74	0,69		4 positive	*Staphylococcus epidermidis*
5	F	MED	71	0,11	6	3 positive	*Staphylococcus hominis*
6	F	PED	14	0,79	29,5	1 positive	*Staphylococcus epidermidis*
7	F	GER	97	255,00		2 neg, 2 pos	*Prevotella oralis*
8	F	GER	80	10,56	247,4	3 positive	*Escherichia coli*
9	M	GER	73	35,80	358,5	1 positive	*Staphylococcus epidermidis*
10	M	MED	40	12,44	573,5	4 positive	*Staphylococcus aureus*
11	M	GER	81	47,78	175,7	2 positive	*Staphylococcus hominis*
12	F	MED	80	14,75		3 positive	*Escherichia coli, Klebsiella oxytoca Clostridium perfrigens*
13	M	MED	77	0,23		4 neg, 1 pos	*Staphylococcus aureus*
14	M	RIAB EUR	81	0,78	130,9	1 positive	*Staphylococcus epidermidis*
15	M	GER	79	4,08	262,5	3 positive	*Escherichia coli*
16	F	MED	58	0,30	171,4	4 positive	*Staphylococcus aurerus*
17	F	GER	69	3,78		4 positive	*Staphylococcus aureus*
18	F	MED	59	0,15	150,3	2 positive	*Staphylococcus epidermidis*
19	F	MED	88	1,74		4 positive	*Escherichia coli*
20	F	MED	59	0,23	134,7	4 positive	*Staphylococcus epidermidis*
21	M	MED	77	30,51	95,6	4 positive	*Staphylococcus pneumoniae*
22	M	MED	66	0,17	157,3	3 neg, 1 pos	*Staphylococcus epidermidis*
23	M	MED	85	352,07	116,9	4 positive	*Escherichia coli*
24	M	MED	81	43,76		2 neg, 2 pos	*Escherichia coli, Enterobacter cloacae*
25	F	MED	80	0,22	148,1	3 neg, 1 pos	*Staphylococcus capitis*
26	F	RIA	54	0,12		8 neg, 1 pos	*Corynebacterium spp.*
27	M	MED	81	1,38	41	4 positive	*Enterococcus faecalis, Enterococcus faecium*
28	F	MAL INF	68	0,19	15,9	4 positive	*Staphylococcus epidermidis*
29	M	MED	64	10,66		3 positive	*Escherichia coli*
30	F	MED	87	0,14	58,5	3 neg, 1 pos	*Staphylococcus aureus*

Paz n°	*Sex*	*Department*	*Age*	*PCT*	*PCR*	*blood culture vials*	*bacterial growth (microorganisms)*
31	F	MED	71	5,75		3 neg, 1 pos	*Staphylococcus epideridis*
32	M	MED	87	0,22	41,2	3 neg, 1 pos	*Escherichia coli*
33	M	MED	47	32,14		4 positive	*Streptococcus pneumoniae*
34	F	MED	61	0,64		4 positive	*Klebsiella oxytoca*
35	M	RIA	72	10,45	115,9	4 neg, 2 pos	*Pseudomonas aeruginosa*
36	F	GER	81	19,23		4 positive	*Escherichia coli*
37	M	GER	90	3,27	173,5	2 neg, 2 pos	*Staphylococcus epiderimdis*
38	M	GER	82	6,40		1 positive	*Streptococcus pneumoniae*
39	M	MED	69	0,93		4 positive	*Escherichia coli, Streptococcus anginosus*
40	F	MED	84	2,32	190,9	2 neg, 2 pos	*Escherichia coli*
41	F	GER	97	3,92	87,9	3 neg, 1 pos	*Escherichia coli*
42	M	RIAB NEUR	66	43,80		2 positive	*Escherichia coli*
43	F	MED	73	0,10	56,5	3 neg, 1 pos	*Staphylococcus epidermidis*
44	F	MED	85	0,68		2 neg, 2 pos	*Staphylococcus hominis*
45	F	GER	71	0,18	325,3	3 neg, 1 pos	*Staphylococcus epidermidis*
46	F	RIA	46	8,80	339	6 positive	*Streptococcus pneumoniae*
47	M	RIAB NEUR	28	8,63		4 positive	*Klebsiella pneumoniae*
48	M	GER	72	5,75	262,8	3 neg, 1 pos	*Staphylococcus capitis*
49	M	RIA	72	24,78	135,8	3 positive	*Proteus mirabilis*
50	F	MED	88	205,82	482	4 positive	*Streptococcus pyogenes, Morganella morganii*
51	F	MED	15	0,43	100,4	3 neg, 1 pos	*Staphylococcus epidermidis*
52	M	RIAB NEUR	28	43,33	163,7	2 neg, 2 pos	*Klebsiella pneumoniae*
53	M	MED	55	0,11	35,4	3 neg, 1 pos	*Staphylococcus epidermidis*
54	M	MED	73	2,75	68,2	4 positive	*Haemophilus influenzae*
55	F	GER	90	56,51	438,5	4 positive	*Staphylococcus aureus*
56	F	MED	52	0,04	44	3 neg, 1 pos	*Staphylococcus epidermidis*
57	M	GER	88	7,13	259,8	3 neg, 1 pos	*Staphylococcus coagulasi negativo*
58	M	MED	67	0,82		3 neg, 1 pos	*Crynebacterium spp.*
59	M	GER	82	1,50		2 neg, 2 pos	*Staphylococcus hominis*
60	F	MED	75	0,82	374,2	2 positive	*Staphylococcus xylosus*
61	M	RIA	61	16,51	93,4	6 positive	*Escherichia coli, Klebsiella pneumoniae*
62	M	MED	65	2,96		3 neg, 1 pos	*Escherichia coli*
63	M	MED	38	0,15	151,4	4 positive	*Staphylococcus haemolyticus*
64	F	MED	16	5,18		2 positive	*Fusobacterium nucleatum*
65	M	MED	70	12,06	191,6	3 neg, 1 pos	*Pseudomonas aeruginosa*
66	F	MED	55	10,59		3 neg, 1 pos	*Staphylococcus epidermidis*
67	M	MED	70	0,35	32,7	1 positive	*Pseudomonas aeruginosa*
68	F	MED	58	0,67		3 positive	*Staphylococcus epidermidis*
69	M	RIA	17	16,38	28	2 positive	*Fusobacterium necrophorum*
70	F	MED	80	2,07		3 neg, 1 pos	*Haemophilus influenzae*
71	F	MED	89	0,13		3 neg, 1 pos	*Staphylococcus epidermidis*
72	F	MED	85	10,98	344,5	3 positive	*Staphylococcus haemolyticus*
73	M	GER	91	5,15	151,8	2 positive	*Serratia marcescens*
74	M	CARDIO	83	26,11		6 positive	*Staphylococcus aureus*
75	M	GER	76	6,60		2 positive	*Staphylococcus aureus*
76	M	MED	88	11,99	57,6	3 neg, 1 pos	*Staphylococcus hominis*
77	M	MED	77	0,11		1 positive	*Staphylococcus epidermidis*
78	F	MED	92	0,12	4,2	2 neg, 2 pos	*Staphylococcus hominis*

Table II. Pathogenic microorganisms identified in bloodcultures.



16, *Staphylococcus hominis* 4, *Staphylococcus aureus* 3, *Escherichia coli* 3, *Corynebacterium spp.* 2, *Enterococcus faecalis* 1, *Enterococcus faecium* 1, *Klebsiella oxytoca* 1, *Streptococcus anginosus* 1, *Staphylococcus xylosus* 1, *Staphylococcus haemolyticus* 1, *Pseudomonas aeruginosa* 1.

The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with intermediate PCT values (from ≥ 2 to <10 ng/mL): *Escherichia coli* 4, *Staphylococcus epidermidis* 2, *Staphylococcus aureus* 2, *Streptococcus pneumoniae* 2, *Haemophilus influenzae* 2, *Klebsiella pneumoniae* 1, *Staphylococcus capitis* 1, *Fusobacterium nucleatum* 1, *Serratia marcescens* 1, *Staphylococcus coagulasi negativo* 1.

The following pathogenic microorganisms were isolated in the positive blood culture vials, associated with high PCT values (≥ 10 ng/mL): *Escherichia coli* 9, *Staphylococcus aureus* 3, *Staphylococcus epidermidis* 2, *Staphylococcus hominis* 2, *Streptococcus pneumoniae* 2, *Pseudomonas aeruginosa* 2, *Proteus mirabilis* 1, *Klebsiella pneumoniae* 2, *Prevotella oralis* 1, *Klebsiella oxytoca* 1, *Clostridium perfrigens* 1, *Enterobacter cloacae* 1, *Streptococcus pyogenes* 1, *Staphylococcus haemolyticus* 1, *Fusobacterium necrophorum* 1, *Morganella morganii* 1 (Table III).

Discussion

PCT testing is increasingly requested by clinicians, as reflected by the significant growth of the requests observed throughout the period considered. Most likely, the increasing interest in this test is due to practical reasons, namely because PCT determination is relatively straightforward and, unlike blood culture tests, it allows a more rapid turnaround time.

Scientific literature confirms that among the inflammatory parameters conventionally used to diagnose infections, PCT offers the best solution for evaluation, monitoring and prognosis of systemic inflammatory response syndromes and sepsis[5-7]. Blood culture tests, on the contrary, provide no information on host response or the onset of organ failure and for a variety

Table III. PCT values and pathogenic microorganisms.

Low PCT values(≤ 2 ng/ml)	Intermediate PCT values(>2 - ≤ 10) ng/ml)	High PCT values(>10 ng/ml)
Staphylococcus epidermidis 16	*Escherichia coli 4*	*Escherichia coli 9*
Staphylococcus hominis 4	*Staphylococcus aureus 2*	*Staphylococcus aureus 3*
Staphylococcus aureus 3	*Staphylococcus epidermidis 2*	*Staphylococcus epidermidis 2*
Escherichia coli 3	*Streptococcus pneumoniae 2*	*Streptococcus pneumoniae 2*
Corynebacterium spp. 2	*Haemophilus influenzae 2*	*Staphylococcus hominis 2*
Enterococcus faecalis 1	*Staphylococcus capitis 1*	*Pseudomonas aeruginosa 2*
Enterococcus faecium 1	*Klebsiella pneumoniae 1*	*Klebsiella pneumoniae 2*
Klebsiella oxytoca 1	*Fusobacterium nucleatum 1*	*Klebsiella oxytoca 1*
Streptococcus anginosus 1	*Serratia marcescens 1*	*Enterobacter cloacae 1*
Staphylococcus capitis 1	*Staphylococcus coagulasi negativo 1*	*Streptococcus pyogenes 1*
Staphylococcus xylosus 1		*Proteus mirabilis 1*
Staphylococcus haemolityticus 1		*Fusobacterium necrophorum 1*
Pseudomonas aeruginosa 1		*Staphylococcus haemolyticus 1*
		Morganella morganii 1
		Prevotella oralis 1
		Clostridium perfrigens 1

of reasons it may even result negative in a minority of septic patients[8].

The data emerged from our study allows us to make draw some conclusions. First, although there is a strong correlation between positive blood culture tests and high PCT values, some positive blood cultures have near to normal levels. This might be due to a potential bacterial contamination by *Stafilococchi coagulasi negativi (*SCN*),* the most frequently isolated strain in the samples with PCT < 2 ng/mL. This hypothesis is supported by the evidence that the only positive blood culture test in the paediatric class concerned the isolation of *Staphylococcus epidermidis*, and corresponded to a very low PCT concentration. Moreover, 11 out of the 16 evidences of *Staphylococcus epidermidis* were isolated on a single vial submitted by the Geriatric ward and Internal Medicine.

As for the negative blood cultures associated with fairly high PCT values, this is not surprising in that high PCT levels are frequently observed in patients with burns, stroke, multiple trauma and cardio circulatory arrest.

Overall, gram-positive blood culture tests were clearly associated with the PCT levels moderately higher than the diagnostic threshold, whereas gram-negative blood cultures were associated with considerably higher levels (Table II). Such difference between plasma PCT values in gram-positive and gram negative infections, is likely due to the different biochemical structure of the microbial components (lipopolysaccharide or endotoxin in gram-negative bacteria and peptidoglycan in gram-positive bacteria), which produce a fairly different immunological and organic response to the infection.

Then, a good agreement was found between negative blood cultures and PCT values, either lower than the diagnostic cutoff or comprised between 2.0 and 10.0 ng/mL, allowing us to conclude that PCT has a high negative predictive value.

PCT is reported to be much more specific and reliable than CRP as regards systemic inflammation. Unlike PCT, PCR increases substantially in localised inflammation, but does not reflect equally well inflammatory condition patterns and provides little prognostic information. In conclusion, we suggest that PCT might be an early marker of systemic infection, which measurement would permit to distinguish inflammation of infective origin, non-infective origin and localised infection from sepsis. Taken together, these specific characteristics of PCT would make its determination suitable to provide important indications for the therapeutic control of infection, contributing to a potential reduction in antibiotic treatment.

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