

Blood Cultures for Community-Acquired Pneumonia: Are They Worthy of Two Quality Measures? A Systematic Review

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BACKGROUND: Obtaining blood cultures (BCs) for patients hospitalized with community-acquired-pneumonia (CAP) has been recommended by experts and used as a measure of quality of care. However, BCs are infrequently positive in these patients and their effect on clinical management has been questioned.

PURPOSE: We performed a systematic review of the literature to determine the impact of BCs on clinical management in CAP requiring hospitalization and thus its appropriateness as a quality measure.

DATA SOURCES: We searched MEDLINE, MEDLINE In-Process, and the Cochrane databases for English-language studies that reported the effect of BCs on management of adults hospitalized with CAP. We also searched the reference lists of included studies and background articles and asked experts to review our list for completeness.

STUDY SELECTION: Studies were chosen if they included adults admitted to the hospital with CAP, BCs were obtained at admission, and BC-directed management changes were reported.

DATA EXTRACTION: We abstracted study design, BC positivity, and frequency of BC-directed management changes.

DATA SYNTHESIS: Fifteen studies, all with observational cohort design, were identified and reviewed. Two included only patients with BCs positive for pneumococcus, yielding 13 studies for the primary analysis. BCs were true-positive in 0% to 14% of cases. They led to antibiotic narrowing in 0% to 3% of patients and to antibiotic broadening ultimately associated with a resistant organism in 0% to 1% of patients.

CONCLUSIONS: BCs have very limited utility in immunocompetent patients hospitalized with CAP. Pneumonia quality measures that include BCs should be reassessed. *Journal of Hospital Medicine* 2009;4:112–123. © 2009 Society of Hospital Medicine.

KEYWORDS: pneumonia, blood cultures, antibiotics, quality measures.

Blood cultures (BCs) have long been a mainstay of the diagnostic evaluation of patients hospitalized with community-acquired pneumonia (CAP). They have been strongly recommended by professional societies^{1–3} and are often expected by admitting physicians. A large retrospective study of Medicare patients with pneumonia found that obtaining BCs is associated with lower mortality.⁴ In 2002, when the National Hospital Quality Measures (NHQM) were introduced, BCs were included as a quality measure for pneumonia.^{5,6}

There was no external funding source for this systematic review.

However, there is uncertainty about the actual utility of BCs in CAP. In large studies they are true-positive in only 7 to 11% of cases and false-positive in ~5%,^{2,7} and whether they affect clinical management has been strongly questioned.⁸⁻¹⁰ Their impact may be limited by slow results, low frequency of bacterial resistance to the empiric antibiotic regimen, and reluctance of physicians to narrow antibiotic coverage.^{9,11} Recent updates to professional society guidelines no longer recommend BCs in all admitted CAP patients.¹²

To evaluate the clinical utility of BCs and the appropriateness of pneumonia quality measures based on BCs, we performed a systematic review of the literature to determine the effect of BCs on the management of adults with CAP requiring hospitalization.

PATIENTS AND METHODS

Data Sources and Searches

We searched the English-language literature via MEDLINE (1966 through September 2007), MEDLINE-In Process, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and ACP Journal Club. Within each of these databases we used keywords and exploded Medical Subject Headings (MeSH) to produce the following search strategy: *blood culture(s)* (keyword), *bacteriological techniques* (MeSH), *blood [microbiology]* (MeSH), *bacteremia [microbiology or drug therapy]* (MeSH), or *diagnostic tests, routine* (MeSH) combined with *pneumonia* (keyword), *pneumonia* (MeSH), *lower respiratory tract infection(s)* (keyword), or *community-acquired infections* (MeSH). To maximize capture of BC or bacteremia studies with subgroups of CAP patients we added the following search strategy: explode *microbiological techniques [utilization]* (MeSH), explode *blood specimen collection [utilization]* (MeSH), or focus *bacteremia [drug therapy]* (MeSH). We reviewed the reference lists of all included studies as well as those of important background articles. Finally, we asked experts to evaluate the completeness of our list.

Study Selection

We included studies in which: (1) subjects were adults hospitalized with CAP; (2) BCs were obtained at or near hospital admission; and (3) the effects of BCs on management (change in an-

tibiotic therapy or other effects such as duration of parenteral therapy, length of hospitalization, or level of care) were reported. The first 2 requirements could be satisfied by a subgroup.

From retrieved citations, relevant abstracts were reviewed, and studies with any potential to meet inclusion criteria were chosen for full-text review. Two authors (N.A., R.S.) independently analyzed each full-text article to determine inclusion for data analysis. A third author (J.T.) analyzed all included and narrowly excluded articles to confirm the final list of included studies. Disagreements were resolved by discussion.

Data Extraction

For the included studies, 2 authors (N.A., K.A.) independently abstracted the following data using a standardized collection instrument: study design and setting, inclusion and exclusion criteria, number of hospitalized CAP patients in whom BCs were obtained, empiric antibiotic regimens, number of true-positive and false-positive BCs, bacteria isolated in true-positive BCs, BC-directed antibiotic narrowing, BC-directed antibiotic broadening ultimately associated with a resistant organism, and any other management effects reported. "Narrowing" refers to coverage of fewer organisms, while "broadening" refers to coverage of a larger or different spectrum of organisms.

If a study included patients not meeting our selection criteria, our analysis was limited to the subset of patients meeting criteria. We also analyzed each study to determine whether a subgroup of severely ill patients was reported separately and whether such a group benefited from BCs. The 2 authors independently repeated all data abstraction to confirm accuracy. We attempted to contact authors for clarification when needed.

Data Synthesis

Data were synthesized by compilation of characteristic summary tables. In the primary analysis, the proportion of positive BCs (both true and false) and the frequency of BC-directed changes in antimicrobial therapy (narrowing, or broadening ultimately associated with a resistant organism) were determined and reported for each study and then described as an aggregate range. This compilation required studies to provide a particular denominator—the number of patients in whom BCs

were performed. If a study did not do so, it was described separately in the secondary analysis, where we also assessed the cost of BCs as well as the impact of BCs in critically ill patients and on outcomes other than antibiotic change. Heterogeneity of subject inclusion and exclusion criteria and empiric antibiotic use were summarized qualitatively. Two authors (N.A., R.S.) assessed each study's quality.

DATA SYNTHESIS

Search Results

Our electronic database search yielded 3236 citations. From this list and the supplementary search of references, we reviewed 607 abstracts; of these, we selected 73 articles for full-text review, and 15 were included in the final analysis (Figure 1). One study was narrowly excluded because it largely included CAP patients that had already been admitted to the hospital and failed an empiric antibiotic trial before BCs were obtained.¹³

Study Characteristics

Fifteen studies with a total of 3898 patients evaluated BC-directed management changes in adults admitted with CAP.^{11,14-27} However, 2 of these, involving only patients with bacteremic pneumococcal CAP, by design could not report the number of patients that had BCs done; thus they were not included in the primary analysis.^{16,25}

The 13 studies amenable to the primary analysis (Table 1) all had an observational cohort design; 6 were prospective^{11,18,20,24,26,27} and 7 were retrospective.^{14,15,17,19,21-23} Sample size varied from 52 to 760 patients. Settings included university and community hospitals in the U.S. and 4 other countries, with patient enrollment spanning the years 1988-2003 (publication dates 1991-2007).

Included patients were usually required to have clinical features of pneumonia and a confirmatory chest x-ray. Treating physicians were required to obtain BCs (either by study or hospital protocol) in only 3 studies^{14,22,24} and in a subgroup of another study,¹¹ otherwise the performance of BCs was left to physician discretion.

Nine studies excluded patients who were immunocompromised,^{11,15,17,18,22-24,26,27} a label that was often incompletely defined. Otherwise, exclusion criteria were variable. Notably, only 3 studies excluded patients admitted to the inten-

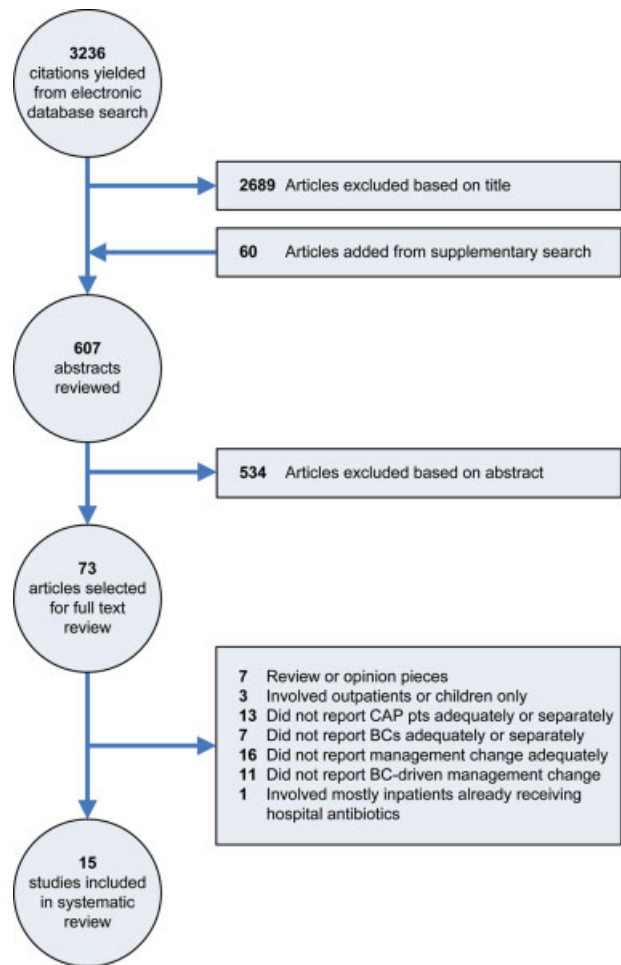


FIGURE 1. Study selection process.

sive care unit (ICU),^{11,18,24} while 6 excluded patients with cancer^{15,17,22-24,27} and 6 excluded either nursing home residents^{15,17,22,26} or the elderly (*de facto* exclusion of most nursing home residents).^{24,27}

Empiric antibiotic regimens, where reported, were predominantly cephalosporin plus macrolide combinations in 4 studies,^{17,22-24} fluoroquinolones in 3 studies,^{11,14,26} and penicillin or 1 of its derivatives in 1 study.²⁷

Concerning the 2 studies not included in the primary analysis, the one by Waterer et al.²⁵ was a retrospective review of all cases of pneumococcal bacteremia (n = 74) associated with an admission diagnosis of CAP (N = 1805) in a US urban hospital over a 3-year period. The one by Chang et al.¹⁶ was a retrospective case-control study of 288 ran-

TABLE 1
Studies of Utility of Blood Cultures in CAP

Study Author, Year, Design, Setting	Inclusion Criteria	Exclusion Criteria	CAP Patients with BCs, n*; True-Positive BCs, n (%); False-Positive BCs, n (%)	BCs Directed Antibiotic Narrowing, n (%)	BCs Directed Antibiotic Broadening and Organism was Resistant, n (%)	Comments
Benenson et al., ¹⁴ 2007; retrospective, U.S. suburban	ED ICD-9 dx and discharge dx of PNA	None	n = 684; 23 (3.4); 54 (7.9)	3 (0.4)	0 (0)	11% of pts with ED dx of PNA not eligible due to different dx at discharge; 25% from nursing homes, 18% recently hospitalized, 14% immunocompromised; Abxs narrowed in 3/21 eligible pts
Ramanjandam Rathlev, ²² 2006; retrospective; U.S. urban	ED, ICD-9, and discharge dx of PNA, and ED BCs before abxs	IC, active cancer, chronic renal failure, hospitalized last 1 week, nursing home resident, aspiration	n = 289; 13 (4.5%); 13 (4.5%)	1 (0.3%)	0 (0%)	532 pts screened; 3% not eligible due to different dx at discharge; of eligible pts, 9% excluded due to HCAP and 31% excluded due to other risk factors; Abxs were narrowed in 1/10 eligible pts; Cost: ~\$8,000 for the 1 pt with abx change
Mountain et al., ²¹ 2006; retrospective, Australian suburban	All pts who had BCs done in the ED during a 2-month period (PNA pts were a subgroup)	None	n = 52; Not reported; Not reported	1 (1.9)	0 (0)	52/218 study pts had clinical PNA. Overall BCs true-positive in 6.4%, false-positive in 7.3%; frequencies for PNA pts not reported separately; Reason for abx change (ceftriaxone to ciprofloxacin) not reported, but thought not to be associated with resistant organism (personal communication); Cost: \$1,950 (U.S.) [†] per BC that altered treatment
Kennedy et al., ²⁰ 2005; prospective, U.S. urban	Clinical and radiographic PNA and BCs in ED or within 3 hours of admission	None	n = 385; 27 (7.0); ~6.0%	11 (2.9)	4 (1.0)	23% of pts from nursing homes, 22% admitted to ICU; 3/4 pts whose abxs were broadened due to a resistant organism came from nursing homes; Abxs were narrowed in 11/19 eligible pts; BCs were false-positive in 25/414 (6%) pts, including 29 pts discharged from the ED
Corbo et al., ¹⁷ 2004; retrospective, U.S. urban	Primary diagnosis of CAP, positive CXR, and ED BCs before abxs	IC, cancer, recent hospitalization, nursing home resident	n = 355; 33 (9.3); 37 (10.4)	7 (2.0)	0 (0)	821 pts admitted with CAP; 24% not eligible due to non-confirmatory CXR, of eligible pts, 22% excluded due to HCAP, 23% excluded due to other risk factors; 6 pts with false-positive BCs had abx change due to BCs - authors suggest hospitalization prolonged in these cases; Physicians "reluctant to narrow" abxs per authors
Campbell et al., ¹¹ 2003; prospective, Canadian multiple (19) hospitals	Two signs or sxms of PNA and positive CXR	IC, shock, direct ICU admission, chronic kidney disease, pregnant or nursing, alcoholism	n = 760; 43 (5.7); Not reported	12 (1.6)	2 (0.3)	38% of pts screened with suspected CAP either ineligible or excluded due to risk factors; Abxs were narrowed in 12/35 eligible pts; In one case, BCs grew MRSA resistant to empiric abxs, but abxs had been changed before BC results available; Cost: \$1550 (U.S.) per BC leading to abx change
Waterer and Wunderink, ²⁶ 2001; prospective; U.S. urban	Signs and sxms of PNA, positive CXR, and BCs before abxs	IC, hospitalized last 30 days, nursing home residents (if non-ambulatory)	n = 209; 29 (13.9); 9 (4.3)	5 (2.4)	1 (0.5)	BCs only changed management in pts in PSI class 4 and 5

(continued)

TABLE 1
(continued)

Study Author, Year, Design, Setting	Inclusion Criteria	Exclusion Criteria	CAP Patients with BCs, n*; True-Positive BCs, n (%); False-Positive BCs, n (%)	BCs Directed Antibiotic Narrowing, n (%)	BCs Directed Antibiotic Broadening and Organism was Resistant, n (%)	Comments
Theerthakarai et al., ²⁴ 2001; prospective, U.S. suburban	Acute febrile illness with respiratory sxms and a positive CXR	IC, cancer; age >65, alcoholism, IVDU, COPD, IDDM, neurologic disease, renal failure, recent abx, severe or complicated PNA	n = 74; 0 (0); 0 (0)	0 (0%)	0 (0%)	Very strict exclusion criteria: 62% of eligible pts excluded due to risk factors; Authors reported that 28% of included pts could have been treated as outpatients per ATS guidelines
Sanyal et al., ²³ 1999; retrospective, U.S. urban	Acute lower respiratory tract infection and positive CXR	IC, cancer, hospitalized last 12 weeks, IVDU, bronchiectasis, splenectomy, not treated per ATS guidelines	n = 174; 19 (10.9); Not reported	Not reported	1 (0.6%)	BC-directed antibiotic changes only reported for pts who did not respond to initial abxs, so BC- directed narrowing could not be determined; The pt whose abxs were broadened was a nursing home resident with severe pneumonia (by ATS criteria)
Glerant et al., ¹⁸ 1999; prospective, French suburban	Acute septic episode with respiratory sxms and positive CXR	IC, ICU admission, hospitalized last 2 weeks, aspiration	n = 53; 5 (9.4); 2 (3.8)	0 (0)	0 (0)	BCs done during first 48 hours so not clear how many BCs sent after hospital abxs started; 23 pts were on abxs before admission; Cost: \$6006 (U.S.), no abx changes
Kelly, ¹⁹ 1998; retrospective, Australian suburban	All pts who had BCs done in the ED over a 9- month period (PNA pts were a subgroup)	None	n = 260; 5%; Not reported	≤1%	≤1%	260/1062 study pts had PNA; 14% of all pts discharged; for CAP pts percentage not reported; False-positive rate 3.8% for all pts, but not reported separately for PNA pts; 1% of PNA pts had abx change due to BCs; type of change not reported, hence reporting of ≤1% in outcome columns; Cost: \$4800 (U.S.) per abx change
Chalasanani et al., ¹⁵ 1995; retrospective; U.S. urban	Dx of PNA, respiratory sxms, positive CXR, and 2 sets of BCs before abxs	IC, cancer, hospitalized last 2 weeks, nursing home resident	n = 517; 34 (6.6); 25 (4.8)	7 (1.4)	0 (0)	1250 pts screened with discharge dx of PNA; 59% either ineligible or excluded due to risk factors (authors did not report number ineligible due to the BC requirement); In one case, BCs grew <i>H.</i> <i>influenzae</i> resistant to empiric abxs, but sputum cultures drove the abx change; Cost: \$4875 per abx change
Woodhead et al., ²⁷ 1991; prospective, British urban (2 hospitals)	Clinical features of CAP and positive CXR	IC, cancer; admitted to geriatric or communicable disease ward	n = 86; 9 (10.5%); Not reported	2 (2.3)	1 (1.2)	8% of pts meeting inclusion and exclusion criteria were later excluded due to different dx at discharge

Abbreviations: ATS, American Thoracic Society; BC(s), blood culture(s); CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; ED, emergency department; HCAP, health care-associated pneumonia (nursing home resident, recent hospitalization); HIV, human immunodeficiency virus; IC, immunocompromised; ICD-9, International Classification of Diseases, 9th version; IDDM, insulin-dependent diabetes mellitus; IVDU, intravenous drug user; PNA, pneumonia; PSI, pneumonia severity index; *S. pneumoniae*, *S. pneumoniae*; abx, antibiotic; dx, diagnosis; pt(s), patient(s); res, resistant; sxm(s), symptom(s).

*n in the column headings always refers to a number of patients.

[†]For brevity we use this abbreviation when a study excluded patients deemed "immunocompromised" and/or excluded patients with HIV, sickle cell disease, or those receiving immunosuppressive therapy.

[‡]Cost figures followed by "(US)" were originally reported in a non-U.S. currency. We converted to US dollars using the currency exchange rate at the time of the study's publication. If the study included nonpneumonia patients, we calculated and reported cost per antibiotic change for the subset of pneumonia patients only.

domly-selected, immunocompetent Medicare patients with bacteremic pneumococcal CAP who survived to discharge. They were matched 1:1 with blood and sputum culture-negative controls to study the rate of fluoroquinolone use at discharge in the 2 groups.

Study Findings

Primary Analysis

As shown in Table 1, BCs were positive for a true pathogen in 0% to 14% of cases. Details of microbiology and empiric antibiotic selection are reported in Table 2. *S. pneumoniae* was by far the most common pathogen: of the 9 studies that had positive BCs and reported the organisms, *S. pneumoniae* represented 50% to 91% of the pathogens, with penicillin-resistance found in 0% to 20%.^{11,14,15,17,18,20,22,23,26} *S. aureus* was next most common, occurring in 6 studies and growing in 3% to 23% of positive BCs;^{11,14,17,20,23,26} its sensitivity to methicillin was reported in 3 studies, with methicillin-resistant *S. aureus* (MRSA) representing 0/3, 3/7, and 1/1 of cases.^{14,20,23} *E. coli* represented 3% to 11% of pathogens in 6 studies,^{11,14,15,20,23,26} while *H. influenzae* represented 2% to 15% of pathogens in 7 studies.^{11,14,15,18,22,23,26}

In the 8 studies that reported false-positive BCs, the false-positive rate was 0% to 10%,^{14,15,17,18,20,22,24,26} with 5 studies finding comparable false-positive and true-positive BC rates^{15,17,20,22,24} and 1 study finding a substantially higher frequency of false-positive than true-positive BCs (Table 1).¹⁴

BCs led to narrowing of antibiotic coverage in 0% to 3% of cases (Table 1). Four studies reported that physicians narrowed antibiotics when BCs indicated that it was possible to do so, but only in 10%, 14%, 34%, and 58% of eligible cases.^{11,14,20,22}

BCs led to antibiotic broadening ultimately associated with a resistant organism in 0% to 1% of cases (Table 1). The pathogens were MRSA (3), methicillin-sensitive *S. aureus* (2), *E. coli* (2), *S. pneumoniae* (1), and Group D Streptococcus (1). Details about these patients' medical histories and demographics were absent or sparse in all but 1 study.²⁰ For several of the above cases it was not explicitly stated that BCs directed the antibiotic changes, though it was usually implied; thus we assumed causation.

Secondary Analyses

In the pneumococcal bacteremia study by Waterer et al.,²⁵ BCs altered management in 31 of the 74 cases of pneumococemia, but in only 2 patients was this associated with antibiotic resistance. Most of the other 29 cases involved narrowing of antibiotics, though switching to penicillin or dropping atypical coverage occurred in only 22% and 37% of eligible patients, respectively. In the study by Chang et al.,¹⁶ there was no significant difference in fluoroquinolone use at discharge between the pneumococemic and culture-negative groups (the primary endpoint), though there was significantly higher β -lactam use and lower macrolide use in the pneumococemic patients at discharge. From the data provided it was not possible to determine how often antibiotic broadening occurred.

Only 2 of the 15 studies stratified management effects based on severity of illness, and neither specified the proportion of severely ill patients admitted to the ICU. Waterer and Wunderink²⁶ prospectively hypothesized that sicker patients were more likely to benefit from BCs. They found that the 30 patients in pneumonia severity index class 5 were most likely to have a BC-driven antibiotic change, though in at most 1 of these patients was associated with a resistant organism. Sanyal et al.²³ stratified patients by severity based on expert guidelines. They found that 19 of 174 patients had severe CAP that did not respond to the initial antibiotic regimen, with 1 having a BC-driven antibiotic change; this was due to resistance.

Only 1 study reported an outcome other than antibiotic change, which in this case was duration of parenteral therapy. In the study, 5 of 43 patients with true-positive BCs remained on intravenous antibiotics for the full course of treatment probably due to bacteremia alone.¹¹

The direct cost of BCs per BC-directed antibiotic change (or total cost of BCs if there was no antibiotic change) was reported in 6 studies and, not adjusted for inflation, ranged from \$1550 to \$8000 (U.S.).^{11,15,18,19,21,22}

Quality of the Studies

A detailed listing of the strengths and weaknesses of each study is provided in the Appendix. Briefly, all 15 studies included in this review were observational. Most did not prospectively require BCs

TABLE 2
Empiric Antibiotics and Microbiology

Study; Author, Year	Empiric Antibiotics Given: Frequency, Agent	Bacteria Isolated in True-Positive BCs; n, Organism	Organisms in BCs Resistant to Empiric Antibiotics
Benenson et al., ¹⁴ 2007	Mild to moderate PNA; levofloxacin; If ICU admission: levofloxacin + azithromycin; If HCAP: levofloxacin + clindamycin; If risk for MRSA: added vancomycin; If structural lung disease: added tobramycin	14 <i>S. pneumoniae</i> ; 3 <i>S. aureus</i> (all MSSA); 2 Group B Strep; 2 <i>H. influenzae</i> ; 1 <i>E. coli</i> ; 1 Group A Strep	None
Ramanujam and Rathlev, ²² 2006	Ceftriaxone + oral azithromycin	11 <i>S. pneumoniae</i> (1 PCN interm res); 2 <i>H. influenzae</i>	None
Mountain et al., ²¹ 2006	Not reported	Not reported completely	None
Kennedy et al., ²⁰ 2005	Not reported	15 <i>S. pneumoniae</i> (3 PCN res); 7 <i>S. aureus</i> (3 MRSA); 3 <i>E. coli</i> ; 1 Coagulase-negative Staph; 1 Pseudomonas; 1 Proteus; 1 Moraxella; 1 <i>E. faecalis</i>	2 MRSA; 1 MSSA (res to levofloxacin, clindamycin); 1 <i>E. coli</i> (res to levofloxacin)
Corbo et al., ¹⁷ 2004	48% ceftriaxone + macrolide; 21% cephalosporin only; 6% quinolone only	30 <i>S. pneumoniae</i> ; 2 <i>S. aureus</i> (# MRSA not reported); 1 Staph haemolyticus	None
Campbell et al., ¹¹ 2003	55% levofloxacin; 45% antibiotic not reported	30 <i>S. pneumoniae</i> (1 PCN res); 5 <i>S. aureus</i> (total # MRSA not reported); 5 <i>E. coli</i> ; 1 <i>H. influenzae</i> ; 1 <i>E. faecalis</i> ; 1 <i>K. pneumoniae</i> ; 1 Enterobacter	1 MRSA (antibiotic changed before BC results available); 1 MSSA (res not reported); 1 <i>S. pneumoniae</i> (PCN res)
Waterer and Wunderink, ²⁶ 2001	60% quinolone only; 25% quinolone + other antibiotic(s)	20 <i>S. pneumoniae</i> (3 PCN res); 3 <i>S. viridans</i> ; 1 <i>H. influenzae</i> ; 1 <i>S. aureus</i> (# MRSA not reported); 1 Enterobacter; 1 <i>E. coli</i> ; 1 Group B Strep; 1 Group D Strep; 1 Group G Strep; 1 Acinetobacter	1 Group D Strep (res to levofloxacin)
Theerthakarai et al., ²⁴ 2001	Cephalosporin + macrolide	None	None
Sanyal et al., ²³ 1999	Severe CAP: erythromycin + ceftazidime or ticarcillin/clavulanate; Nonsevere CAP: 76% cefuroxime + erythromycin, 18% cefuroxime only	14 <i>S. pneumoniae</i> (0 PCN res); 2 <i>H. influenzae</i> ; 1 <i>S. aureus</i> (MRSA); 1 <i>K. pneumoniae</i> ; 1 <i>E. coli</i>	1 MRSA
Glerant et al., ¹⁸ 1999	Not reported	4 <i>S. pneumoniae</i> (0 PCN res); 1 <i>H. influenzae</i>	None
Kelly, ¹⁹ 1998	Not reported	Not reported	Cannot determine
Chalasanit et al., ¹⁵ 1995	Not reported	29 <i>S. pneumoniae</i> (0 PCN res); 3 <i>H. influenzae</i> ; 1 <i>S. pyogenes</i> ; 1 <i>E. coli</i>	<i>H. influenzae</i> (sputum culture drove the antibiotic change) <i>E. coli</i> (res to erythromycin)
Woodhead et al., ²⁷ 1991	78% included penicillin, aminopenicillin, or amoxicillin/clavulanate; 33% included erythromycin; 21% β-lactam + erythromycin	Not reported separately for BCs	Not reported
Chang et al., ¹⁶ 2005	BC+ /Controls: 34%/21%/Quinolones; 86%/88%/β-lactam; 1%/1%/Amox/PCN; 38%/37%/Macrolide	288 <i>S. pneumoniae</i> (only organism, by design)	Not reported
Waterer et al., ²⁵ 1999	38% Cephalosporin + macrolide ± other; 27% Quinolone ± other	74 <i>S. pneumoniae</i> (only organism, by design); 11 PCN interm res; 4 PCN res	2 <i>S. pneumoniae</i> (both resistant; degree of resistance not specified)

Abbreviations Grp, group; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; PCN, penicillin; interm, intermediate; res, resistant; Staph, staphylococcus; Strep, streptococcus.

in all patients admitted with CAP. This could have biased the results in favor of BC utility as physicians presumably order BCs in patients with a higher probability of bacteremia. Conversely, several studies did not explicitly require two sets of BCs or that BCs be done prior to antibiotics, so they may not have revealed the maximum utility of BCs. The 2 studies limited to pneumococcal bacteremia and described in the secondary analysis were inherently biased against BC utility, as pneumococcus is more likely to be antibiotic-sensitive than other CAP pathogens.

Eligibility was based only on an emergency department (ED)/admission diagnosis of CAP, a criteria that approximates real world practice, in 3 studies.^{19,21,25} The other studies required either a confirmatory radiograph or a hospital discharge diagnosis of pneumonia. Consequent ED/admission misdiagnosis rates were 3%, 8%, 11%, 24% in the 4 studies that reported them;^{14,17,22,27} the final diagnoses, when reported, were nearly all noninfections or proximal respiratory tract infections.^{22,27}

Five studies included all eligible patients.^{14,19–21,25} However, 3 studies excluded 23%, 31%, and 62% of eligible patients based on risk factors for bacteremia or resistant pathogens,^{17,22,24} and the rest did not report the number excluded.

DISCUSSION

Summary of Findings

Our systematic review of the literature finds that BCs rarely alter empiric antibiotic therapy in adults hospitalized with community-acquired pneumonia. Even when there is a change in treatment it usually is not of the type most likely to impact patient outcome, which is antibiotic broadening ultimately associated with a resistant organism. In the 13 studies that could quantify this effect, it occurred in only 0% to 1% of cases in which BCs were obtained. Antibiotic narrowing occurred in 0% to 3% of cases, with physicians often choosing not to narrow antibiotics when BC results suggested that they could do so.

Limits on BC Utility

β-Lactam-Resistant *Pneumococcus*

In the studies reviewed here 50%-90% of positive BCs grew pneumococcus, consistent with the 60% to 67% rate reported elsewhere.^{2,28,29} Pneumococci that invade the bloodstream have disproportionately

low rates of β -lactam resistance,^{30,31} inherently limiting the utility of BCs for detecting inadequate empiric antibiotic therapy. Though pneumococcal resistance to β -lactams has risen over the last 2 decades, third-generation cephalosporins, preferred agents for CAP, are still extremely effective. Even when the organism is by historical standards moderately resistant to them, these cephalosporins at standard doses maintain bactericidal efficacy in the lung,^{32,33} and their use in the setting of such resistance is not associated with higher mortality.^{34–37} By newer laboratory standards 97% and 96% of *S. pneumoniae* isolates in mid-2003 were sensitive to ceftriaxone and cefotaxime, respectively.³⁸ Thus a major potential benefit of BCs—detecting cephalosporin-resistant pneumococcus—remains a rare occurrence.

Polymicrobial Infection

If positive BCs in CAP mostly reveal antibiotic-sensitive pathogens, one may infer that at least they lead to narrowing of therapy. However, the studies reviewed here reveal that this usually does not happen.

One explanation for this reluctance to narrow antibiotics is that CAP is often a polymicrobial disease. When rigorous serologic testing is done, multiple pathogens are found in up to 40% of cases.³⁹ The occult copathogen is frequently an intracellular one and thus cannot be detected by BCs. Though the evidence for empirically treating these atypical organisms is mixed,^{40,41} expert guidelines recommend doing so,¹² and guideline-concordant antibiotic therapy in CAP is associated with lower mortality.⁴² Even in bacteremic pneumococcal CAP, monotherapy is associated with higher mortality.^{43–46} Thus, stopping antibiotic coverage of atypical pathogens in response to BCs alone might not always be appropriate.

Prognosis

Another rationale given for ordering BCs is that bacteremic pneumonia is a morbid disease so positive BCs may demand prolonged parenteral therapy or extended hospitalization. Although mortality for bacteremic pneumococcal pneumonia (the predominantly studied variety of bacteremic pneumonia) has historically been high at ~20%,^{47,48} studies that have examined pneumococcal bacteremia as an independent risk factor for death in CAP have yielded mixed results.²

Moreover, it appears that patients with bacteremic pneumococcal pneumonia who reach clinical stability may be safely switched to oral antibiotics.⁴⁹

It is not clear that positive BCs in pneumonia (at least in the case of *S. pneumoniae*) should alter the duration of parenteral therapy or hospitalization, though whether or not such effects occur in clinical practice was largely unaddressed by the studies reviewed here.

Epidemiology

One theoretical benefit of BCs is their epidemiologic value. When true-positive in pneumonia, perhaps more than any other test they identify with great specificity at least 1 of the causative agents. Unfortunately, as discussed above, BCs alone provide an incomplete and skewed picture of the microbiology of CAP. They underestimate atypical organisms, overestimate pneumococcus, and, because bacteremic pneumococcus is more likely to be antibiotic-susceptible, they underestimate antibiotic resistance.¹¹ Tracking pathogens in bacteremic pneumonia may be useful nonetheless, but perhaps a more accurate method for determining etiologic trends is periodic comprehensive microbiological investigation, including BCs, sputum/bronchial cultures, and serology.

Costs

In the studies reviewed here, based on reported costs of \$15 to \$65 per set of BCs or per patient, BCs cost \$1550 to \$8000 (U.S.) per BC-directed antibiotic change. Considering that very few of these antibiotic changes involved broadening associated with a resistant organism, the cost/benefit ratio was quite high. Today BCs may be even more expensive, as U.S. hospitals now often charge over \$150 per set of BCs.^{50,51}

The cost of false-positive BCs must also be taken into account. The false-positive rate in the studies reviewed here was 0% to 10%, similar to that reported elsewhere.⁷ False-positive BCs increase hospital length of stay by 3 to 5 days and hospital charges by \$4400 to \$8800.^{51,52}

Limitations of the Review

Our search strategy was designed to be sensitive and included backup methods such as searching article references and querying experts. Nevertheless, we may have missed studies, especially if there were small eligible subgroups or if determin-

ing management effects was not a primary purpose. We chose not to measure instances of antibiotic broadening that were not associated with a resistant organism, though in unusual cases (eg, *Pseudomonas* bacteremia) this effect of BCs may be useful.

The methodologies of the included studies were adequate to measure the key outcomes with reasonable validity. Biases were evident, though they occurred both for and against BC utility.

Eligibility varied across studies, and most investigations excluded immunocompromised or other high-risk patient groups, which could have biased results against BC utility. However, results of these studies were consistent with those that included all patients with CAP, suggesting the degree of bias was probably small. Still, given this concern, it would be prudent not to generalize the findings of this review to immunocompromised patients. Moreover, although the critically ill and those who today would be classified as having healthcare-associated pneumonia (HCAP)—nursing home residents, the recently hospitalized, and hemodialysis patients—were included in most studies, their numbers were small, and these groups were not analyzed separately; thus, the results might not be generalizable to these populations either. Finally, the reported studies, which enrolled patients through 2003, do not reflect more recent increases in the prevalence of resistant pathogens, such as MRSA, in the community.

BCs as a Quality Measure

The adoption of BCs as a quality measure was largely predicated on the widely-cited study by Meehan et al.,⁴ which showed an association between BC obtainment and reduced mortality. This study, which associated processes of care with hard outcomes such as mortality, was limited by uncontrolled confounders, including variation in hospital quality.⁵³ A more recent study of pneumonia processes of care found no association between BC collection and mortality.⁵⁴ Another study often cited to support BC use, by Arbo and Snyderman,⁵⁵ showed that positive BCs were associated with changes in antibiotic therapy, but it included very few pneumonia patients and did not describe results for them separately.

The inclusion of BC acquisition in 2 quality measures in the NHQM guidelines for pneumonia impacts the clinical practice of hospitals and phy-

sicians, which may be rated and reimbursed differentially based on their compliance with such measures. One of the quality measures requires BCs in patients admitted to the ICU. The other requires that ED BCs for pneumonia, if obtained, be drawn before antibiotics are given.⁶

The studies we reviewed are not specific to these quality measures, but are relevant to them. With regard to the first measure, all but 3 studies included patients admitted to the ICU and found BCs to be of minimal benefit overall. Our subgroup analysis of severely ill patients was unrevealing. The ICU measure is tentative in its validity, but it is not unreasonable given that these patients have a life-threatening infection and may be at risk for bacteremia with resistant pathogens.¹²

The second measure, though perhaps simply seeking to maximize the potential for BCs to turn positive, depends for its validity on BCs being useful in a large proportion of patients with CAP. Though we cannot exclude the possibility that BCs benefit certain subsets of patients, such as those who are immunocompromised or have HCAP, our findings do not support obtaining BCs in all or even most adults hospitalized with CAP. This conclusion is reflected in the 2007 Infectious Diseases Society of America/American Thoracic Society management guidelines for CAP, which state that BCs are optional except for patients with severe pneumonia, some immunocompromised states, and particular radiographic abnormalities.¹²

With such data and guidelines in mind, a physician seeking to minimize treatment delays in a patient with pneumonia may give antibiotics early in the ED course (the basis of another quality measure) without obtaining BCs. If she later determines that the patient is particularly high-risk for bacteremia or a resistant pathogen, should she be discouraged from ordering BCs? Experts specifically state that BCs, even after antibiotics, are warranted for such a patient.¹²

With the scope of medical practice captured in quality measures being so narrow, having 2 measures based on a test with such limited benefit is itself questionable.

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