International survey of Paediatric Infectious Diseases consultants on the management of community-acquired pneumonia complicated by pleural empyema

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Running head: A survey of antibiotics for empyema

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Abstract

Aim: Community-acquired pneumonia (CAP) complicated by pleural empyema is an important paediatric problem. Antibiotic management decisions are made on the basis of little available data and without strong specific recommendations in guidelines.

Methods: Online survey of paediatric infectious diseases (PID) physicians disseminated by major international professional organizations, examining empiric and targeted antibiotic choice, switch to oral antibiotics, and duration of treatment for two hypothetical cases of contrasting severity.

Results: 183 responses, most from North America, Western Europe and Australia/New Zealand. Increased disease severity was significantly associated with broader-spectrum and combination empiric and targeted antibiotic treatment, empiric methicillin-resistant *Staphylococcus aureus* (MRSA) coverage, and both longer intravenous (IV) and total duration of antibiotic treatment. Empiric MRSA coverage was also associated with local prevalence. Clinical progress was most important for determining timing of switch from IV to oral antibiotics. Few respondents chose antibiotics with activity against organisms associated with atypical pneumonia (e.g. *Mycoplasma*, *Chlamydia*), and most did not choose agents inhibiting protein synthesis (e.g. clindamycin), even in the case of severe invasive group A streptococcal infection. Some variation in targeted treatment

choices reflected areas of uncertainty such as *Streptococcus pneumoniae* susceptibility breakpoints, comparative effectiveness of anti-staphylococcal penicillins and 1st generation cephalosporins for serious *S. aureus* infections, and linezolid and vancomycin for MRSA pneumonia.

Conclusions: This international survey of PID physicians highlights priority targets for clinical research to improve antibiotic treatment of CAP complicated by empyema. Interventions which might be studied include empiric antibiotic guidelines stratified by case severity, adjunctive empiric use of agents inhibiting protein synthesis (e.g. clindamycin), and approaches to encourage rapid IV-to-oral switch and shorter total antibiotic treatment.

Keywords: community-acquired pneumonia; pleural empyema; antibiotic therapy

Introduction

Pleural empyema is a well-recognized complication of community-acquired pneumonia (CAP) in children and adolescents. The microbiology of empyema associated with CAP is relatively restricted (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, methicillin-susceptible and resistant *Staphylococcus aureus*) compared to CAP without empyema, where viruses and bacteria associated with ‘atypical’ pneumonia are often implicated.^{5, 6} Intervention studies have largely concentrated on choice and timing of procedural intervention (thoracotomy, thoracocentesis, chest tube drainage with or without fibrinolysis, and thoracoscopy).⁷⁻¹¹

Antibiotic recommendations in guidelines make few specific recommendations regarding drug choice, route, and duration, and where recommendations are made these are inconsistently applied.^{7, 10-16} Patients with empyema receive extended antibiotic courses, risking development of antibiotic

resistance, *Clostridium difficile* disease, adverse drug reactions, and vascular access complications, with associated burdens for patients, carers, and health systems. Paediatric Infectious Diseases (PID) specialists have a role in developing institutional guidelines, directing antimicrobial stewardship efforts, and are frequently consulted to optimize antibiotic therapy for patients with complicated respiratory tract infections, often with limited evidence to guide decision-making¹⁷. There is continuing uncertainty regarding key aspects of antibiotic management of empyema: empiric regimen choice, especially the appropriate epidemiological and clinical thresholds for recommending coverage of methicillin-resistant *S. aureus* (MRSA) and/or *S. pneumoniae* with reduced susceptibility to beta-lactam antibiotics; use of adjunctive antibiotics inhibiting protein synthesis such as clindamycin; timing of switch from intravenous to oral antibiotics; and duration of antibiotic treatment. The aim of this study was to explore the approach of PID physicians to antimicrobial management of CAP complicated by empyema using an online case-based survey.

Methods

An online case-based survey, drawing on the authors' clinical experience, was prepared and reviewed by the North American Pediatric Infectious Diseases Society (PIDS), European Society of Paediatric Infectious Diseases (ESPID), and Australian and New Zealand Paediatric Infectious Diseases (ANZPID) subgroup of the Australasian Society of Infectious Diseases. After revisions, ANZPID and PIDS endorsed the survey (Supplemental Content 1) and it was approved by ESPID. Each group advertised the survey in a minimum of three repeated emails to their respective memberships. At the time, ESPID and PIDS estimated they had approximately 1000 members each, and ANZPID had approximately 50 active members. More precise figures were unavailable, and these estimates included full-time researchers and laboratory microbiologists, retired physicians, pharmacists, students, and others not targeted for this survey. Only members identifying as a PID consultant or fellow (i.e. in a subspecialty Paediatric Infectious Diseases training program) were eligible to participate in the study.

Participants were presented with two cases (Box). If a respondent did not complete the entire survey, answers were included when they had completed at least the first case. For each case, questions addressed choice of empiric and targeted antibiotics and, following a report of steady uncomplicated improvement, timing of switch from intravenous to oral antibiotics and total duration. Respondents were limited to pre-determined tick-box answers, but could choose "other" to add free text as an alternate response.

For the analysis, some antibiotics were grouped by class for clarity (e.g. anti-staphylococcal penicillins), and 'penicillin' is used to encompass penicillin G and aminopenicillins. For methicillin-

resistant *S. aureus* (MRSA), terms used were non-multiresistant (nmMRSA), referring to isolates with a traditionally ‘community-acquired’ antibiotic susceptibility profile (e.g. susceptible to clindamycin, trimethoprim-sulphamethoxazole, tetracyclines), and multiresistant (mMRSA) for isolates with ‘hospital-acquired’ susceptibility (e.g. vancomycin, linezolid, ceftaroline). ‘Atypical coverage’ was defined as any regimen including a macrolide, fluoroquinolone, or tetracycline antibiotic. The protein-synthesis inhibitors clindamycin, linezolid, and rifampin were considered ‘anti-toxin’ agents, although separate considerations such as tissue penetration, bioavailability, and MRSA coverage may be alternative reasons for choosing these drugs.

Results are presented as frequencies and proportions, with p-values for comparisons between discrete categories of severity, geography, estimated local MRSA prevalence, and awareness of guidelines, generated by two-tailed Fisher’s exact test using R (version 3.3.1), with a p-value <0.05 considered statistically significant.¹⁸ As a measure of spread, drug utilisation 50% (DU50%) and 90% (DU90%) were calculated separately for empiric therapy in both cases (number of different antibiotics accounting for 50% and 90% of all prescriptions).¹⁹

Data were collected and managed using REDCap electronic data capture tools hosted at the Murdoch Children’s Research Institute²⁰. The project was approved by the Royal Children’s Hospital Melbourne Human Research Ethics Committee (reference number 34342). Participation was voluntary and anonymous.

Results

Respondents

There were 183 responses from May 30th to October 8th 2015 (Table I), 169 of which were complete from first to last question. Most respondents were PID consultants (82%) at metropolitan specialist children's hospitals (80.9%) with local guidelines for management of empyema (65%), in North America, Western Europe, Australia or New Zealand (78.1%). Pneumococcal conjugate vaccine was in the local immunization schedule for 86.9% of respondents. *Haemophilus influenzae* type b conjugate vaccine was given in all represented countries. Estimated local MRSA prevalence was less than 10% in 44.8% of responses, and some European respondents commented that their local rate was closer to 1%.

Empiric antibiotic therapy

In the ward case, 29 different empiric regimens were selected almost equally distributed between monotherapy and dual-agent therapy, amounting to 270 individual antibiotic prescriptions (Table II). The DU50% was two antibiotics (third generation cephalosporins, penicillin). The DU90% was six antibiotics (Table, Supplemental Content 2). For the ICU case, there were 57 different empiric regimens. Combination treatment was favored. There were 391 antibiotic prescriptions (Table II). The DU50% was two antibiotics (third generation cephalosporins, vancomycin) and the DU90% was eight antibiotics (Table, Supplemental Content 2).

Empiric coverage of MRSA was significantly more frequent in the severe case (Table II) and with increasing clinician-perceived local MRSA prevalence (Figure 1). North American respondents reported very high local MRSA prevalence (40/62, 64.5% reporting >25% local MRSA prevalence) compared to respondents from Australia/New Zealand and Western Europe (Figure, Supplemental Content 3). For the ward case, North American respondents were more likely to cover MRSA

(43/62, 69.4%) than those from Australia/New Zealand (12/25, 48%) and Western Europe (15/56, 26.8%) (P=0.018). In the ICU case, all respondents from North America and Australia/New Zealand covered MRSA, compared to 42/53 (79.2%) from Western Europe (P<0.001). Empiric use of 'anti-toxin' agents (mostly clindamycin) was also more frequent in the severe case as was 'atypical' coverage (Table II).

Empiric use of agents with extended Gram negative and/or anaerobic coverage (piperacillin-tazobactam, ceftazidime, cefepime, ciprofloxacin, meropenem, aminoglycosides, metronidazole) was higher for the ICU case than the ward case (47/177, 26.6% versus 7/183, 3.8%, P<0.001). Use of these drugs did not differ significantly in either the ward or ICU case between respondents who were either aware or unaware of institutional guidelines for antibiotic treatment of empyema.

Targeted antibiotic therapy

Targeted monotherapy was preferred for every organism in both cases, though there was considerable variability in chosen regimens (Table III). Combinations and broader-spectrum antibiotics were more frequently used in the ICU case, not accounted for by increased adjunctive use of 'anti-toxin' agents.

Narrow-spectrum penicillins were preferred over cephalosporins in regimens (monotherapy or combinations) for penicillin-susceptible *S. pneumoniae* in the ward case (149/183 regimens including penicillin, 81.4% versus 22/183 including a cephalosporin, 12%; P<0.001) and ICU case (116/171, 67.8% versus 39/171, 22.8%; P<0.001). Conversely, third-generation cephalosporins were preferred over penicillin in regimens for *S. pneumoniae* with penicillin MIC=4mg/mL, for the ward (118/183,

64.5% versus 30/183, 16.4%; $P<0.001$) and ICU case (112/171, 65.5% versus 21/171, 12.3%; $P<0.001$).

Penicillin monotherapy for group A *Streptococcus* was preferred to combination therapy with clindamycin in the ward and ICU cases. An 'anti-toxin' agent (mostly clindamycin) was selected significantly more frequently in the ICU case than the ward case (51/171, 29.8% versus 28/183, 15.3%; $P=0.001$).

For MSSA, regimens including an anti-staphylococcal penicillin (e.g. naf-, oxa-, clox-, flucloxacillin) were favoured over first-generation cephalosporins (e.g. cefazolin), in the ward (138/183, 75.4% versus 25/183, 13.7%; $P<0.001$) and ICU case (121/171, 71% versus 21/171, 12.3%; $P<0.001$). For nmMRSA, clindamycin monotherapy was a significantly more frequent choice in the ward case compared to vancomycin monotherapy (109/183, 59.6% versus 27/183, 14.8%; $P<0.001$). For the ICU case, clindamycin monotherapy was selected by a similar number of respondents as chose vancomycin monotherapy (49/171, 28.7% versus 42/171, 24.6%; $P=0.46$). For mMRSA, vancomycin monotherapy was preferred over linezolid monotherapy in the ward case (104/183, 56.8% versus 29/183, 15.8%; $P<0.001$) and the ICU case (75/171, 43.9% versus 29/171, 17.0% ; $P<0.001$). There were significant regional differences in linezolid use (monotherapy or in combinations) for the ward case (Australia/New Zealand: 13/25, 52% versus Western Europe: 21/52, 40.4% versus North America: 12/62, 19.4%; $P=0.004$) and ICU case (Australia/New Zealand: 16/24, 66.7% vs Western Europe: 21/46, 45.7% vs North America: 15/60, 25.0%; $P=0.001$).

Intravenous-to-oral switch and total duration

Respondents were significantly more likely to favor switch to oral antibiotics based on clinical progress (as opposed to a pre-defined duration) and shorter total duration of treatment in the ward case (Table IV).

Discussion

Findings of this international survey of PID physicians regarding CAP complicated by empyema highlight avenues for future clinical research and should encourage efforts aimed at curbing unnecessarily broad-spectrum antibiotic therapy, early consideration of switching from intravenous to oral antibiotics, and shorter duration of treatment. Current guidelines highlight the lack of evidence to guide antibiotic decision-making, emphasizing the need to empirically cover common pathogens according to local resistance patterns but making few strong or specific recommendations regarding drug choice, timing of switch to oral antibiotics, and total duration.^{7, 8, 10, 12} This uncertainty was reflected by wide variability in antibiotic decision-making for the two hypothetical cases in this survey.

A 2011 survey of 141 North American PID physicians by Hersh et al. also found wide variation in empiric antibiotic recommendations for children hospitalized with uncomplicated and complicated CAP, only partly explained by local resistance patterns.¹⁶ For empyema, 95% selected a regimen including a 2nd or 3rd generation cephalosporin, only rarely as monotherapy (7% chose beta-lactam monotherapy). Macrolides were included by 21.4%, higher than in either case in this survey. An anti-MRSA agent was included by 90.7%, 40% choosing clindamycin as the only MRSA-active drug regardless of local resistance rates. As in this survey, there was a significant association between participant-reported MRSA prevalence and empiric coverage, from 50% when MRSA prevalence

was <10% to 94% when it was >50%. These comparatively higher rates likely reflect the high profile and prevalence of MRSA in North America.²¹ The narrower range of antibiotics in the survey by Hersh et al. did not include aminoglycosides, carbapenems, anti-pseudomonal penicillins, 4th and 5th generation cephalosporins. Very few respondents to this current survey chose these unnecessarily broad agents in the ward case. There was greater use of meropenem and piperacillin-tazobactam (usually with vancomycin) for the ICU case, possibly reflecting protocolized approaches to severe sepsis. Hersh et al. concluded that better knowledge of local and condition-specific resistance patterns was required to guide empiric treatment. This survey highlights severity as another important consideration, balancing infection- and treatment-related benefits and risks.

Unexpected heterogeneity was observed in targeted treatment, most evident for the ICU case. Well recognized points of uncertainty contributed to some variability, such as discordant guidance between the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *S. pneumoniae* with penicillin MIC=4mg/mL.^{22, 23} More concerning was the frequent choice of unnecessarily broad regimens such as third-generation cephalosporins for penicillin-susceptible *S. pneumoniae*, the most common cause of pleural empyema. This was not accounted for by use of adjunctive ‘anti-toxin’ agents such as clindamycin, which was unexpectedly low across all the scenarios including for GAS septic shock, despite the relatively strong evidence for severe streptococcal infections.^{24, 25}

Anti-staphylococcal penicillins were preferred over 1st generation cephalosporins for MSSA reflecting a persisting belief in their superiority as suggested by *in vitro* studies, despite recent

clinical studies finding equivalence, lower cost, and reduced adverse drug effects for cefazolin compared to nafcillin.^{26, 27} Clindamycin monotherapy was the most frequent choice for nmMRSA, even for the bacteraemic ICU scenario, though it is not rapidly bactericidal and initial monotherapy for septic patients is generally discouraged.²⁸ Vancomycin was preferred to linezolid for mMRSA. Linezolid use increased for the ICU case and was much more frequent amongst respondents from Australia/New Zealand and Western Europe, possibly reflecting uncertainty regarding the role of Panton-Valentine leukocidin and other virulence factors.²⁹ Linezolid has well-advertised theoretical pharmacological and practical advantages over vancomycin, although favorable findings from industry-sponsored trials have not been widely accepted.³⁰⁻³² It is also expensive, can cause significant adverse effects, and its bacteriostatic activity means it is not preferred for use as monotherapy in bacteraemic patients. There is little paediatric experience with ceftaroline and it was a very uncommon choice. It may become an important drug for targeted treatment of highly resistant pneumococcal and staphylococcal infections.³³

There was a preference in this survey for individualized antibiotic treatment guided by clinical progress, informed in part by inflammatory markers, with early consideration of intravenous-to-oral switch, and total duration determined by severity and response. Even for the life-threatening case, without further complications most respondents chose a total duration of only 2-3 weeks. There are no data from prospective studies to guide clinicians in determining duration of treatment.³⁴ As reported by Gonzalez et al. in a retrospective study of 169 children with empyema, the mode of procedural intervention and complications such as necrosis and abscess often influence antibiotic treatment decisions.³⁵ Recent recommendations have suggested as few as seven days of antibiotics may be adequate after clinical improvement (chest drain removal, resolution of fever, weaning

supplemental oxygen).^{34, 35} However, as McMullan et al. point out in their systematic review and guideline for timing of intravenous-to-oral switch and total treatment duration for many infections, fever may persist for several days despite adequate treatment and extended antibiotic courses of up to six weeks are sometimes used depending on severity, complications, progress, and residual disease after drainage.³⁴ McMullan et al. and many guidelines encourage consideration of early switch to oral antibiotics upon clinical improvement.^{7, 10-12, 34} In a multicenter retrospective cohort study by Shah et al. including 2123 children with complicated pneumonia, treatment failure rates were similar for children treated with oral antibiotics at discharge compared to those treated with outpatient intravenous antibiotics, who had more adverse drug reactions, line-related complications, and unplanned revisits.³⁶

Limitations of this study include the low response rate (likely <20%), similar to other surveys of subspecialists.³⁷ The results may not be fully representative, though we believe they justify our broad qualitative findings. MRSA prevalence was determined only by respondent report and may not have always been correct, though treatment decisions are likely to be associated with perceived rather than actual resistance rates. Some respondents commented that they would have appreciated more details regarding antibiotic susceptibility, procedural interventions, intraoperative findings, and imaging to determine their approach to route and duration of treatment, underlining the finding that PID physicians are looking to individualize antibiotic management. In most hospitals, general paediatricians, respiratory specialists and intensivists make many of the decisions included in this survey, and these groups were not included. However, PID specialists drive development of antibiotic guidelines, coordinate AMS efforts, and frequently consult on severe and microbiologically-confirmed cases, especially for antibiotic resistant organisms.

Conclusions

The findings of this international survey of Paediatric Infectious Diseases physicians highlight important questions for future clinical research to improve antibiotic treatment for children with community-acquired pneumonia complicated by empyema. Non-procedural interventions to study could include: empiric guidelines stratified by severity; restriction of empiric MRSA coverage to patients with severe sepsis and hospitals with extremely high MRSA prevalence (i.e. >50% of community-acquired *S. aureus* infections); adjunctive empiric ‘anti-toxin’ therapy; and early IV-to-oral switch and shorter-course antibiotic treatment.

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Box. Ward and ICU cases

A previously-well fully-immunised 3-year-old girl presents with community-acquired pneumonia...

Ward case (moderately unwell)	ICU case (critically ill)
<ul style="list-style-type: none">• Fever, tachypnoea, tachycardia• Hypoxic, requiring 2 L/min low-flow oxygen via nasal prongs• Right lower lobe pneumonia with effusion on examination and chest x-ray• Leukocytosis, neutrophilia, CRP>100 mg/L, procalcitonin > 2ng/mL, not bacteraemic• Procedural intervention on day 2 of admission (VATS or chest tube +/- fibrinolysis not specified)	<ul style="list-style-type: none">• Fever, respiratory failure, septic shock• Fluid resuscitation, pressors, intubation, near-maximal respiratory support (ECMO considered)• Right-sided “white-out” with a large effusion and possible early cavitation on chest x-ray• Leukopenia, neutropenia, CRP>100 mg/L, procalcitonin > 2ng/mL, bacteraemia (organism not specified)• No evidence of extra-pulmonary septic foci• Chest tube in ICU – drainage of copious pus

VATS: video-assisted thoroscopic surgery, ICU: intensive care unit, CRP: C-reactive protein, ECMO: extra-corporeal membrane oxygenation

Table I. Respondent characteristics

N = 183	Frequency	(%)
Professional experience		
Consultants	150	(82.0)
> 20 years at this level	26	(14.2)
10-20 years	54	(29.5)
5-9 years	31	(16.9)
1-4 years	39	(21.3)
Fellows	33	(18.0)
Organisational membership		
Only ESPID	92	(50.3)
Only PIDS	58	(31.7)
Only ANZPID	16	(8.7)
ANZPID & ESPID	11	(6.0)
PIDS & ESPID	5	(2.7)
AZPID & PIDS	1	(0.5)
Region of current employment		
North America	62	(33.9)
Western Europe	56	(30.6)
Australia/New Zealand	25	(13.7)
Eastern Europe	14	(7.7)
Asia	14	(7.7)
Central and South America	6	(3.3)
Africa	3	(1.6)
Middle East	3	(1.6)
Local guidelines for empyema management		
Yes	119	(65.0)
No	61	(39.9)
Don't know	3	(1.6)
Estimated local MRSA prevalence		
<10%	82	(44.8)
10-25%	42	(23.0)
26-50%	31	(16.9)
>50%	17	(9.3)
Don't know	11	(6.0)
Routine pneumococcal conjugate vaccination		
13-valent	141	(77.0)
10-valent	14	(7.7)
7-valent	4	(2.2)
No	24	(13.1)

ANZPID: Australian and New Zealand Paediatric Infectious Diseases group; ESPID: European Society of Paediatric Infectious Diseases; MRSA: methicillin-resistant *Staphylococcus aureus*; PIDS: Pediatric Infectious Diseases Society

Table II. Empiric antibiotic therapy

	Ward, n = 183 (%)		ICU, n = 177 (%)	P
monotherapy	93 (50.8)		14 (8.5)	<0.001
2 antibiotics	86 (47.0)		100 (56.5)	NS
3 antibiotics	4 (2.2)		57 (32.2)	<0.001
4 antibiotics	0 (0)		6 (3.4)	0.014
nmMRSA coverage	72 (39.3)		154 (87.0)	<0.001
mMRSA coverage	31 (16.9)		126 (71.2)	<0.001
‘atypical’ coverage	6 (3.3)		19 (10.7)	0.006
‘anti-toxin’ agent(s)	41 (22.4)		70 (39.5)	<0.001
Top 5 empiric regimens				
1.	Penicillin	45 (24.6)	CEPH 3 + Vancomycin	39 (22.0)
2.	CEPH 3 + Clindamycin	27 (14.8)	CEPH 3 + Clindamycin + Vancomycin	24 (13.6)
3.	CEPH 3 + Vancomycin	27 (14.8)	Meropenem + Vancomycin	12 (6.8)
4.	CEPH 3	23 (12.6)	CEPH 3 + Clindamycin	11 (6.2)
5.	Amoxicillin-clavulanate	15 (8.2)	PIP-TZ + Vancomycin	6 (3.4)

CEPH 3: third generation cephalosporins; ; ICU: intensive care case; nmMRSA: non-multiresistant methicillin-resistant *Staphylococcus aureus*, with 'community-acquired' susceptibility profile; mMRSA: multiresistant methicillin-resistant *Staphylococcus aureus*, with 'hospital-acquired' susceptibility profile; ‘atypical’ coverage: macrolides, tetracyclines, fluoroquinolones; ‘anti-toxin’ agents: clindamycin, rifampicin, linezolid; NS: not statistically significant; PIP-TZ: piperacillin-tazobactam

Table III. Most common regimens for targeted treatment

Organism	Ward, n=183 (%)		ICU, n=171, (%)	
<i>S. pneumoniae</i> (penicillin MIC < 2mg/mL)	penicillin	149 (81.4)	penicillin	103 (60.2)
	CEPH 3	21 (11.5)	CEPH 3	32 (18.7)
<i>S. pneumoniae</i> (penicillin MIC = 4mg/mL)	CEPH 3	105 (57.4)	CEPH 3	81 (47.4)
	penicillin	28 (15.3)	CEPH 3 + vancomycin	21 (12.3)
<i>S. pyogenes</i>	penicillin	125 (68.3)	penicillin	81 (47.4)
	penicillin + clindamycin	19 (10.4)	penicillin + clindamycin	44 (25.7)
methicillin-susceptible <i>S. aureus</i>	AS PCN	128 (69.9)	AS PCN	88 (51.5)
	CEPH 1	19 (10.4)	AS PCN + clindamycin	21 (12.3)
non-multiresistant methicillin-resistant <i>S. aureus</i>	clindamycin	109 (59.6)	clindamycin	49 (28.7)
	vancomycin	27 (14.8)	vancomycin	42 (24.6)
multiresistant methicillin-resistant <i>S. aureus</i>	vancomycin	104 (56.8)	vancomycin	75 (44.1)
	linezolid	29 (15.8)	linezolid	29 (17.1)

MIC: minimum inhibitory concentration; ICU: intensive care unit; AS PCN: anti-staphylococcal penicillin (naf-, oxa-, clox-, flucloxacillin); CEPH 1, 3: first, third generation cephalosporin

Table IV. Intravenous to oral switch and duration of antibiotic therapy

	Ward, n=183 (%)	ICU, n=169 (%)	P
Intravenous-to-oral switch^A			
Entire course IV	2 (1.1)	9 (5.3)	0.0295
At least 2 weeks IV	16 (8.7)	57 (33.7)	<0.001
Switch when WBC/CRP normal	53 (29.0)	77 (45.6)	0.0014
Switch now	111 (60.7)	26 (15.4)	<0.001
Stop all antibiotics	1 (0.5)	0 (0)	NS
Total antibiotic duration^B			
14 days	117 (63.9)	30 (17.8)	<0.001
21 days	49 (26.8)	74 (43.8)	0.0011
28 days	14 (7.7)	54 (32.0)	<0.001
42 days	3 (1.8)	11 (6.5)	NS

CRP: C-reactive protein; IV: intravenous; ICU: intensive care unit case; NS: not statistically significant; Ward: ward case; WBC: leukocyte count

A - Ward case: day 5, 24 hours post chest tube removal, last fever or oxygen requirement; ICU case: day 7, 48 hours post chest tube removal, intermittent low-grade fever, 0.5 L/min oxygen requirement

B - Ward case: day 10, continuing clinical improvement, normal inflammatory markers; ICU case: day 14, continuing clinical improvement, near-normal inflammatory markers. No reference to causative organism or previous intravenous-to-oral switch choice.

Figure I. Empiric anti-MRSA coverage

MRSA: methicillin-resistant *Staphylococcus aureus*; None: no antibiotic with anti-MRSA activity in regimen; Limited: coverage for non-multiresistant MRSA only (e.g. clindamycin, trimethoprim-sulphamethoxazole, tetracyclines); Full: coverage for multiresistant MRSA (e.g. vancomycin, teicoplanin, linezolid, ceftaroline)

A previously-well fully-immunised 3-year-old girl presents with community-acquired pneumonia...

Ward case (moderately unwell)	ICU case (critically ill)
<ul style="list-style-type: none"> • Fever, tachypnoea, tachycardia • Hypoxic, requiring 2 L/min low-flow oxygen via nasal prongs • Right lower lobe pneumonia with effusion on examination and chest x-ray • Leukocytosis, neutrophilia, CRP>100 mg/L, procalcitonin > 2ng/mL, not bacteremic • Procedural intervention on day 2 of admission (VATS or chest tube +/- fibrinolysis not specified) 	<ul style="list-style-type: none"> • Fever, respiratory failure, septic shock • Fluid resuscitation, pressors, intubation, near-maximal respiratory support (ECMO considered) • Right-sided “white-out” with a large effusion and possible early cavitation on chest x-ray • Leukopenia, neutropenia, CRP>100 mg/L, procalcitonin > 2ng/mL • Bacteremia (organism not specified) • No evidence of extra-pulmonary septic foci • Chest tube in ICU – drainage of copious pus

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What is already known on this topic

- Bacteria responsible for paediatric community-acquired pneumonia complicated by pleural empyema include *Streptococcus pneumoniae*, *Streptococcus pyogenes*, methicillin-susceptible and resistant *Staphylococcus aureus*.
- Children with pleural empyema often require procedural intervention (i.e. video-assisted thoracoscopic surgery, VATS, or chest tube drainage with or without fibrinolysis).
- Lengthy antibiotic courses are often given, but few specific recommendations exist to guide empiric and definitive antibiotic choice, timing of intravenous-to-oral switch, and total duration of treatment.

What this paper adds

- For children with pleural empyema who are not critically-ill, Paediatric Infectious Diseases physicians favour narrower-spectrum empiric antibiotic regimens, early switch from intravenous to oral antibiotics based on clinical progress, and total duration of treatment of 3 weeks.
- There are opportunities to study interventions such as empiric antibiotic guidelines for pleural empyema stratified by severity, use of adjunctive antibiotics inhibiting protein synthesis such as clindamycin, rapid intravenous-to-oral switch, and shorter total antibiotic treatment duration to reduce unnecessary antibiotic use, adverse drug effects, and complications of prolonged venous access.

International survey of Paediatric Infectious Diseases consultants on the management of community-acquired pneumonia complicated by pleural empyema

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Running head: A survey of antibiotics for empyema

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