



Research article

Inter-expert agreement on indications for antibiotic therapy in older adults admitted to French hospital through an emergency department



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HIGHLIGHTS

- Experts from different disciplines showed substantial agreement in deciding on the requirement of antibiotics
- The level of inter-expert agreement depended on the physicians' medical specialties
- Most of the bacterial infections were lung infections and urinary tract infections
- This study is the first step towards to better identification of infections with an atypical presentation of infections

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ABSTRACT

Background: Around one third of older adults with infections have an atypical presentation upon admission to an emergency department (ED).

Objective: To evaluate the level of agreement between experts from several disciplines on the indication for antibiotic therapy for a bacterial infection in older patients presenting at an ED, and to describe the characteristics of the infections.

Methods: Based on comprehensive medical records, three experts (a geriatrician, an emergency physician (EP), and an infectious disease specialist (IDS)) determined independently and then jointly whether a patient presenting at the ED had a bacterial infection requiring antibiotic therapy. Inter-expert agreement was expressed as a fixed-marginal Fleiss' kappa (κ).

Results: Of the 444 medical records included, the consensus meeting found that 114 (25.7%) had an indication for antibiotics, 327 (73.6%) did not have an indication, and 3 could not be classified. The overall level of agreement was 85.2%, and κ [95%CI] was 0.64 [0.57–0.72] ($p < 0.001$). The level of agreement between the geriatrician and the IDS (89.41%, κ 0.73, 95%CI [0.62–0.85] ($p < 0.001$)) was higher than that between the geriatrician and the EP (83.56%, κ 0.62, 95%CI [0.51–0.73] ($p < 0.001$)) and between the IDS and the EP (82.66%, κ 0.59, 95%CI [0.48–0.70] ($p < 0.001$)). The levels of agreement between the final adjudication, was higher for the geriatrician, and IDS respectively 94.1% (κ 0.85, 95%CI [0.74–0.97] ($p < 0.001$)) and 94.4% (κ 0.86, 95%CI [0.74–0.97] ($p < 0.001$)). 114 (25.7%) patients had a bacterial infection (mostly lung infections ($n = 55$, 48.2%) and urinary tract infections ($n = 25$, 21.9%)), and 28 patients (6.3%) had a viral infection.

Conclusion: Our results highlighted substantial agreement between members of a multidisciplinary expert panel.

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1. Introduction

It has been estimated that by 2050, one third of the French population will be over the age of 60 and 15.6% will be over the age of 75 [1]. Population aging and worsening access to primary care and outpatient care are driving an increase in admissions to emergency departments (EDs). In France, 21.8 million patients visited an ED in 2018 – a mean annual increase of 3.6% since 1996 [2]. According to the literature, patients aged 75 or over account for 8.5–12% of ED visits [3, 4].

In one study, 28.6% of older patients with infections had an atypical presentation upon admission to the ED [5]. Emergency physicians have little time to assess older patients in the ED. Furthermore, samples for bacteriologic testing are not always collected during the patient's often short stay in the ED. The combination of these three factors makes it difficult to diagnose a definite bacterial infection on discharge from the ED. This diagnostic difficulty might increase the risk of antibiotic overuse, underuse or misuse in older patients [6, 7].

Studies of the specific features of infections in older patients in EDs are based on the diagnoses established by physicians in the ED or on retrospective analyses of coded data [5, 8, 9]. However, simple coding is not always a reliable method for evaluating diagnoses and/or identifying the factors associated with bacterial infections in older patients. We therefore developed a new method for the diagnosis of bacterial infections, based on a multidisciplinary review of medical records (MRs).

The objective of the present study was to validate the method by measuring the level of agreement between members of a multidisciplinary expert panel with regard to the indication for antibiotic therapy of a bacterial infection in older patients presenting at the ED, through a retrospective review of the patients' MRs. The secondary objective was to describe the characteristics of bacterial and viral infections observed in older patients admitted to hospital through the ED.

2. Material and method

2.1. Participants

We conducted an observational, single-center study of a retrospective cohort of elderly patients (aged 80 or over) admitted to Tours University Medical Center Tours, France) through the general ED in 2018. In order to describe the seasonal distribution of infections, we selected all MRs during the first three days of each month. We excluded the MRs of patients had been admitted directly to hospital wards or through cardiology, psychiatry, and gynecology EDs (i.e. without passing through the general ED), patients admitted to psychiatric units, and patients who refused the re-use of their personal medical data. Patients discharged to home were also excluded, due to a lack of data on outpatient follow-up.

2.2. Definition of a established bacterial infection on admission to the ED

The multidisciplinary expert group comprised a geriatrician, an emergency physician, and an infectious disease specialist, i.e. corresponding to the medical specialties typically involved in the routine care of elderly patients with infections. The group therefore had a good overview of older patients and their care. All three experts had clinical experience in the ED. The emergency physician and the infectious disease specialist also had some clinical experience in a geriatric department, and the geriatrician had some clinical experience in an infectious disease department. The geriatrician, the emergency physician, and the infectious disease specialist had respectively three, six and four years of experience in their specialty.

The experts' role was to determine whether a given patient met the primary endpoint, i.e. presentation of a bacterial infection on arrival at the ED and that required the initiation of antibiotic therapy in the ED or during the subsequent hospitalization (yes, no, not classifiable). The experts were also asked to define the type of infection (bacterial or viral) and the site of infection upon the patient's arrival at the ED. The expert's

adjudications were based on comprehensive, detailed MRs for the hospital stay (from ED admission to hospital discharge), in order to obtain the most reliable outcome possible. The study's goal was not to put the experts in a real-life situation in the ED. In order to limit the time it took for the experts to adjudicate the cases, each set of MR was preformatted.

The experts had to define the primary endpoint independently. All discordant cases were then reviewed jointly, in order to reach a consensus on the primary endpoint.

2.3. Statistical analysis

The level of inter-expert agreement on the primary outcome was expressed as a fixed-marginal Fleiss' kappa (κ) [10] with a 95% confidence interval represent the sampling error. The results were interpreted according to Landis and Koch Koch's guidelines (Appendix 1) [11]. The two-modality Fleiss' kappa was expressed with prevalence and bias indexes that respectively represent the prevalence of the event among experts and the disagreement rate among experts, as suggested by Sim and Wright [12].

2.4. Ethics and patient information

No nominative patient data were collected; the study involved the re-use of anonymized data. As a retrospective study of routine clinical practice, the present analysis fell within the scope of France's MR-004 reference methodology; approval by an institutional review board and informed consent were not required. However, the study was approved by a hospital committee with competency for research not requiring approval by an institutional review board (Tours University Medical Center; reference: 2020–049). Furthermore, the study database was registered with the French National Data Protection Commission (*Commission nationale de l'informatique et des libertés* (Paris, France); reference: 4909120620 and MR-004 2205437v0).

3. Results

3.1. Population

We included 444 (57%) of the 779 MRs on older patients having attended the ED at least once over the study period (Figure 1 and Table 1). The main exclusion criterion was discharge to home (279 out of 335; 83.3%). The median [interquartile range (IQR)] age was 87 [84–91], and the male:female sex ratio was 0.66. The study patients had relatively few comorbidities; the Charlson Comorbidity Index (not adjusted for age) was ≤ 3 for 290 (65.3%) patients. 333 (75%) of the patients were living in the community, and 69 (15.5%) were living in a nursing home. The median [IQR] number of MRs in the first three days of the month was 37 [32–40]. The median [IQR] length of hospital stay was 7 [4–11] days. The patients were transferred from the ED to medical wards ($n = 294$ patients (66.2%)), short-stay care units ($n = 72$ (16.2%)) and surgical units ($n = 62$ (14%)).

3.2. Adjudication of bacterial infections

In the independent expert analysis, 77 (17.3%) of the 444 MRs were assigned as having a bacterial infection with an indication for antibiotic therapy, and 276 (62.2%) did not have an indication for antibiotic therapy (Table 2). The consensus meeting enabled the assignment of 91 (20.5%) MRs with disagreements; 37 (40.7%) were considered to have a bacterial infection with an indication for antibiotic therapy, and 51 (56%) were considered not to have an indication. After the independent analysis and the consensus meeting, 114 (25.7%) MRs were considered to have an indication for antibiotic therapy, 327 (73.6%) were considered not to have an indication, and three (0.7%) could not be classified (due to a lack of information) (Figure 1).

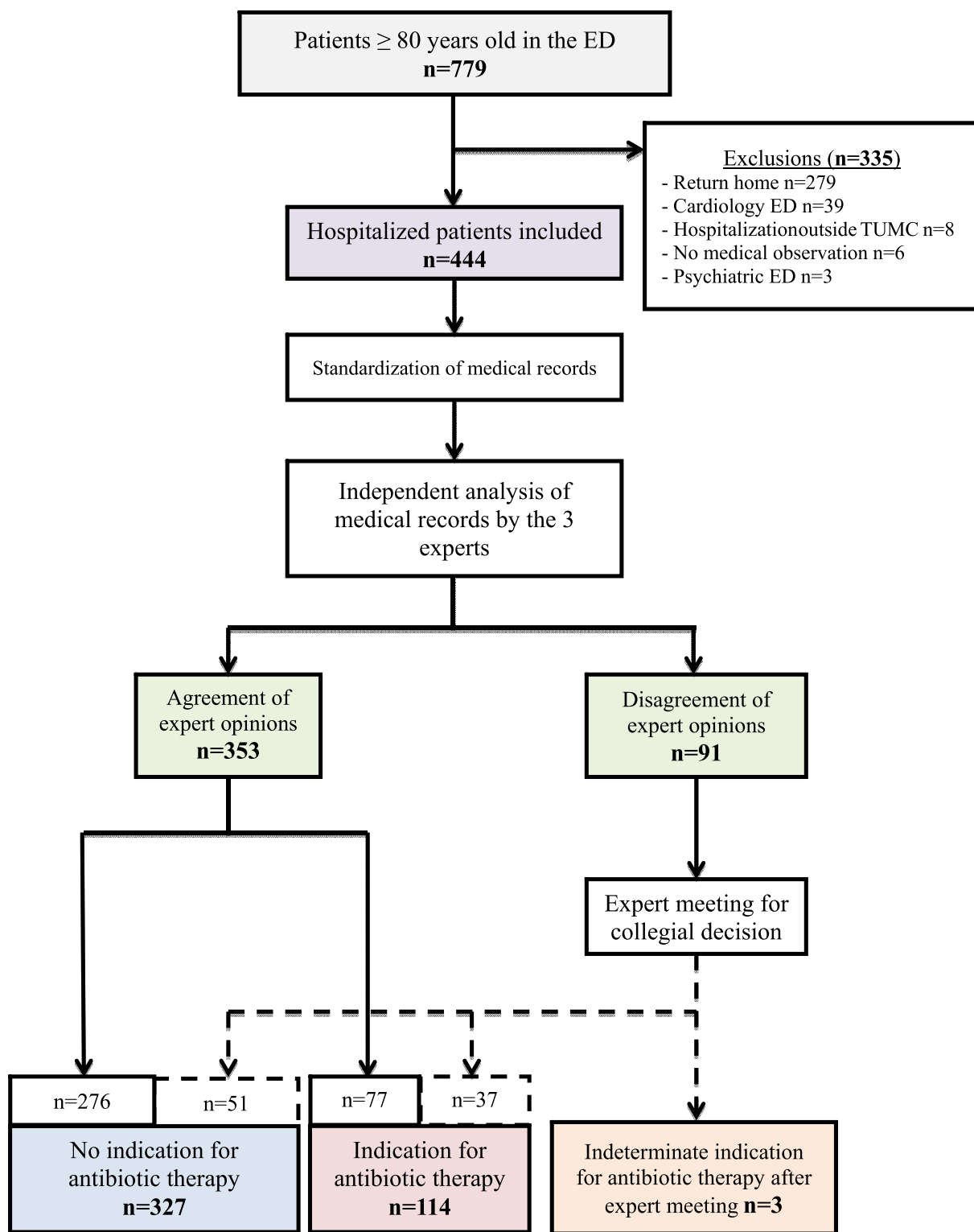


Figure 1. Study flow chart. ED: emergency department; TUMC: Tours University Medical Center.

3.3. Inter-expert agreement

In the independent analyses, the three experts had determined the same primary outcome for 353 (79.5%) of the patients. Overall, Fleiss' κ [95% confidence index (CI)] was 0.64 [0.57–0.72] ($p < 0.001$), and the percentage agreement (according to the κ equation) was 85.2%. After removal of the 33 patients who could not be classified by to at least one

expert (leaving $n = 411$ to be analyzed), Fleiss' κ coefficient was 0.75 95%CI [0.67–0.83] ($p < 0.001$) and the overall agreement of 90.6%.

The side-by-side analysis showed higher agreement between the geriatrician and the infectious disease specialist (89.41%, κ 0.73, 95%CI [0.62–0.85] ($p < 0.001$); prevalence index 0.51; bias 0.03) than between the geriatrician and the emergency physician (83.56%, κ 0.62, 95%CI [0.51–0.73] ($p < 0.001$); prevalence index 0.46; bias 0.04) and between

Table 1. Population characteristics.

	n = 444	%
Age (years) median [IQR]	87 [84–91]	
Sex ratio (Male/Female)	177/267	
Living place		
Home	333	75
Nursing home	69	15.5
Residential home	39	8,8
Other	3	0,7
Month of admission		
January	52	11.7
February	38	8.6
March	49	11.0
April	38	8.6
May	37	8.3
June	33	7.4
July	26	5.8
August	46	10.4
September	27	6.1
October	27	6.1
November	34	7.7
December	37	8.3
Charlson Comorbidity Index (excluding the age item)		
Median [IQR]	3 [1–4]	
Score 0	53	11.9
Score 1-3	237	53.4
Score 4-10	150	33.8
Score >10	4	0.9
Post-emergency services		
Medical departments	294	66.2
Short-term hospitalization department	72	16.2
Surgical department	69	15.6
Intensive care unit	9	2

IQR: interquartile range

Table 2. The individual experts' assignments and the types of infections, according to the final assignments.

	Indication for antibiotics		
	YES	NO	NC
Final decision: n (%) assigned	114 (25.7)	327 (73.6)	3 (0.7)
Individual assignment: n (%) assigned			
Emergency physician	122 (27.5)	302 (68)	20 (4.5)
Geriatrician	116 (26.1)	324 (73)	4 (0.9)
Infectious Disease Specialist	100 (22.5)	333 (75)	11 (2.5)
Type of bacterial or viral infection, n (% of all infections)			
Pulmonary	55 (38.8)	21 (14.8)	/
Urinary	29 (20.4)	/	/
Digestive	12 (8.5)	3 (2.1)	/
Dermatological	7 (4.9)	/	/
Endocarditis and bacteremia	6 (4.2)	/	/
Osteoarticular	5 (3.5)	/	/
Other	/	4 (2.8)	/
Total	114 (80.3)	28 (19.7)	/

NC: not classifiable

the infectious disease specialist and the emergency physician (82.66%, κ 0.59, 95%CI [0.48–0.70] ($p < 0.001$); prevalence index 0.49; bias 0.06) (Figure 2).

Analysis of agreement between the final adjudication and the emergency physician, the geriatrician, and the infectious disease specialist

was respectively 84% (κ 0.63, 95%CI [0.52–0.73] ($p < 0.001$); prevalence index 0.47; bias 0.04), 94.1% (κ 0.85 95%CI [0.74–0.97] ($p < 0.001$); prevalence index 0.48; bias 0.01) and 94.4% (κ 0.86 95%CI [0.74–0.97] ($p < 0.001$); prevalence index 0.51; bias 0.03) (Figure 3).

The 2-modality analysis (yes, no) showed higher Fleiss's κ than for the 3-modality analysis (yes, no, undefined) with a median [IQR] increase of 0.08 (0.06–0.09) (Figures 2 and 3).

3.4. Analysis of discordant cases

When considering the 91 discordant cases, the geriatrician and the emergency physician determined more indications for antibiotic therapy (42.9% (n = 39) and 49.5% (n = 45), respectively) than the infectiologist did (25.3%, n = 23). The infectious disease specialist and the emergency physician defined more undefined indications (12.1% (n = 11) and 22% (n = 20), respectively) than the geriatrician did (4.4%, n = 4). 52 (57.1%) of the discordant cases were considered to have an infection (37 bacterial infections (71.2%) and 15 viral infections (28.8%)). Most of the infections in discordant cases were lung infections (n = 37, 71.2%).

3.5. Epidemiologic characteristics of bacterial and viral infections

With regard to the 114 MRs with a bacterial infection upon presentation at the ED, the experts identified 55 lung infections (48.2%), 29 urinary tract infections (25.5%), 12 digestive tract infections (10.5%), 7 skin infections (6.1%), 6 cases of bacteriemia or endocarditis (5.3%), and 5 bone and joint infections (4.4%) (Table 2). 50 of the 114 MRs with a bacterial infection (as defined by the experts) had a positive microbial culture. There were 14 positive blood cultures (two of which were positive for two or more pathogens), with four positive for *Staphylococcus aureus*, three for *Escherichia coli*, three for *Enterococcus faecalis*, one for *Enterococcus faecium*, two for *Streptococcus agalactiae*, one for *Streptococcus massiliensis*, one for *Streptococcus pneumoniae*, one for *Clostridium perfringens*, and one for *Bacteroides faecis*. 27 of the MRs with a urinary tract infection had a positive urine culture (one of which was positive for two or more pathogens), with 22 positive for *Escherichia coli*, 2 for *Proteus mirabilis*, 2 for *Enterococcus faecalis*, 1 for *Klebsiella oxytoca*, and 1 for *Klebsiella pneumoniae*. Five MRs had a positive pneumococcal urine antigen test, and one sputum culture was positive for *Pseudomonas aeruginosa*. Of the patients transferred to surgical wards, seven had positive intraoperative specimens: three for *Escherichia coli*, one for *Prevotella intermedia*, one for *Staphylococcus aureus*, one for *Klebsiella pneumoniae*, and one for an unidentified Gram-negative bacterium.

Solely viral infections were defined for 28 of the 444 MRs; these included 21 lung infections, 3 digestive tract infections, and 4 infections at other sites. Respiratory multiplex PCRs showed viral coinfection in 8 of the 55 bacterial lung infections (14.5%) and 2 of the 29 urinary tract infections (6.8%). PCR tests of respiratory tract samples variously revealed influenza virus (n = 12 out of 20; 60%), metapneumovirus (n = 3; 15%), rhinovirus (n = 2; 10%), coronavirus (n = 1; 5%) and respiratory syncytial virus (n = 1; 5%), and a PCR test of a feces sample revealed norovirus (n = 1; 5%).

4. Discussion

Our results highlighted the substantial level of agreement between three experts with regard to the identification of an indication for antibiotic therapy for a bacterial infection in older patients admitted to hospital through the ED. An inter-expert analysis shows that the correlation between the emergency physician's adjudications and the other two experts' adjudications was slightly lower than the other correlations. Similarly, a comparison between the individual experts and the final (consensus) adjudication showed that the correlation was greater for the geriatrician and the infectious disease specialist. The observed differences might result from several factors.

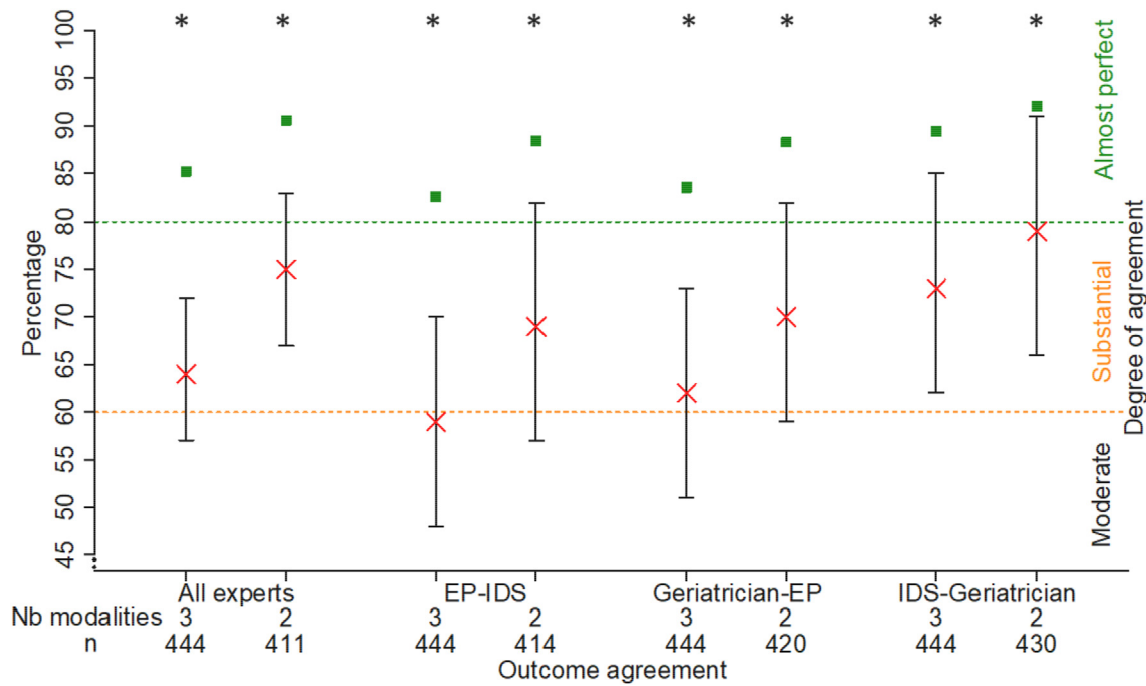


Figure 2. Evaluation of the level of agreement between the experts (independent adjudications). Graphical representation of the percentage agreement (green squares) and Fleiss' κ (red crosses) with the 95%CI (error bars), expressed as a percentage, for all experts, between the emergency physician (EP) and the infectious disease specialist (IDS), between the geriatrician and the EP, and between the IDS and the geriatrician. The results are presented for three classification modalities (yes/no/not classifiable) or two modalities (yes/no). The degree of agreement (right-hand scale) was interpreted according to Landis and Koch's guidelines (11). n: number of patients. * $p < 0.001$.

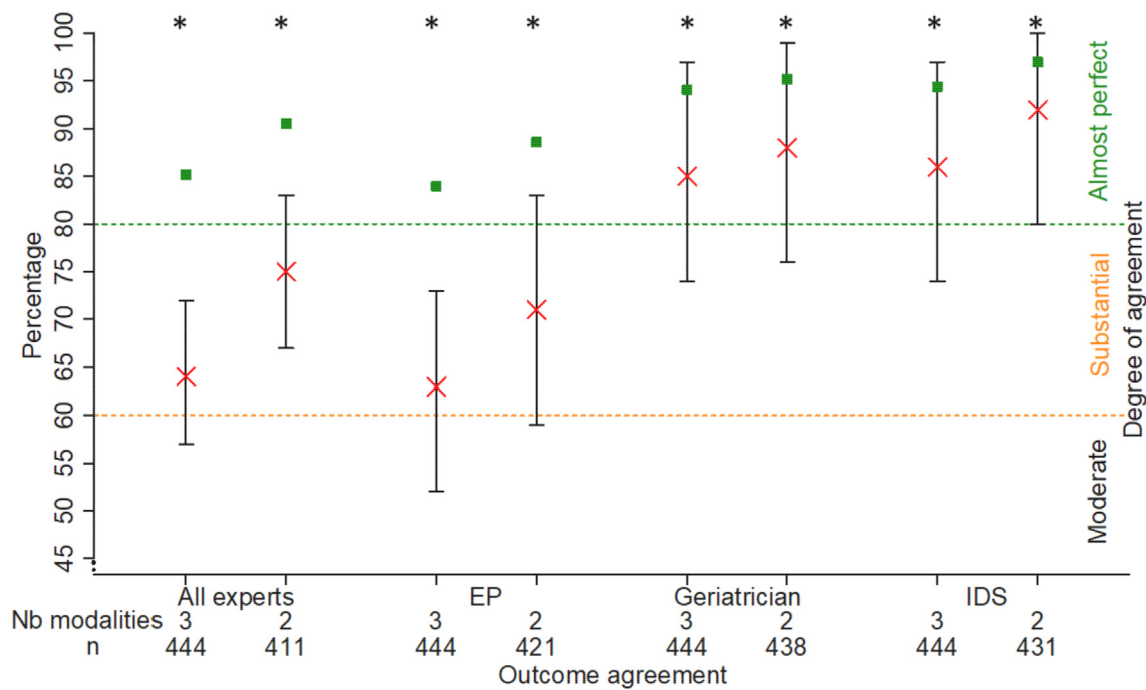


Figure 3. Evaluation of the degree of agreement between the experts and the final adjudication. Graphical representation of the percentage agreement (green squares) and Fleiss' κ (red crosses) with the 95%CI (error bars), expressed as a percentage, for the experts as a whole and for each expert (emergency physician (EP), infectious disease specialist (IDS), and geriatrician) vs. the final (consensus) adjudication. The results are presented for three classification modalities (yes/no/not classifiable) or two modalities (yes/no). The degree of agreement (right-hand scale) was interpreted according to Landis and Koch's guidelines (11). n: number of patients. * $p < 0.001$.

Firstly, each practitioner (although an expert in his/her field) analyzes a case through the prism of his/her specialty and personal experience, rather than on knowledge alone [13,14,15]. When the experts

analyzed the MRs independently, they had to deal with a degree of uncertainty prompted by the question “what would I have done in this situation?”. The resulting cognitive reasoning generates one or more

hypotheses for subsequent analysis by the expert [15, 16, 17, 18]. Thus, it is possible that for certain atypical clinical presentations and in the absence of definitive bacteriologic test results, the emergency physician prioritized data available at the time of the visit to the ED and the other two experts prioritized the data on the course of the disease during the hospital stay. Likewise, the infectious disease specialist might have been more aware of the problem of bacterial multiresistance associated with the widespread use of antibiotics and so might have preferred to delay the initiation of antibiotic therapy early. Indeed, in discordant cases, the infectious disease specialist was less likely than the emergency physician and the geriatrician to adjudicate an indication for antibiotic therapy (25.3%, 49.5%, and 42.9%, respectively). In routine clinical practice in the ED (where there is uncertainty about the presence or absence of a bacterial infection in a population of older, often frail patients), the patient benefit/risk ratio might indicate the introduction of empiric antibiotic therapy because of (i) the elevated risk of mortality associated with the late treatment [19] of atypical presentations of severe infection [20, 21], and (ii) the option of withdrawing antibiotic therapy within 24–48 h of transfer from the ED (i.e. when the bacteriologic test results are typically received).

Secondly, the majority of the infections in the discordant cases were lung infections (71.2%, $n = 37$). This type of infection is particularly difficult to diagnose (especially in older patients [8]), due to the lack of reliable radiologic data (CT scans, etc.) [22], the frequent absence of laboratory test results [23], higher severity scores [24], and a high prevalence of viral co-infection [25,26,27].

Thirdly, the adjudication process was complex, and the experts might have taken some time to adapt to it. The adjudication was designed in order to avoid wrongly designating MRs with an indication for prophylactic antibiotic therapy (pneumocystis or prior to surgery) or an infection not requiring antibiotic therapy (urinary tract colonization or a viral infection). Moreover, it was specified that antibiotic therapy could be initiated at any time during the hospital length of stay (and not necessarily in the ED), so as not to (i) favor empiric antibiotic therapy and (ii) ignore bone and joint infections (for which antibiotic therapy is deferred until after surgical samples have been taken) or non-severe urinary tract infections (requiring targeted treatment, depending on the antibiotic susceptibility profile).

Inspection of Fleiss's κ showed that the level of agreement was higher for a 2-modality (yes/no) adjudication. This result depends on the equation used to calculate κ [11] but corresponds to the "real-life" situation in which the physician must always decide whether or not to initiate antibiotic therapy. Thompson and Walter [28] suggested that the validity of the Kappa coefficient depends on the prevalence index. Thus, a very high or very low prevalence index will increase the likelihood that experts will agree with each other. In our study, the prevalence index was intermediate (between 0.46 and 0.51) and so is unlikely to have significantly influenced the Kappa coefficient. Similarly, Thompson and Walter [28] suggested that the study population should be as close to reality as possible, so that prevalences were as similar as possible. Our study's recruitment (throughout 2018) was intended to be as representative as possible of the "real-life" prevalence of bacterial infections in elderly subjects hospitalized via the emergency department. Feinstein and Cicchetti [29] suggested that a high bias index leads to a higher kappa coefficient, whereas a low bias index leads to a lower kappa coefficient. In our study, the low bias index observed for all experts (<0.1) indicates that the study population was relatively homogeneous that the kappa coefficient was lower. We are not aware of published data on multidisciplinary expert evaluations of the diagnosis of bacterial infection with an indication for antibiotic therapy, and therefore our results cannot be compared with the literature.

It is noteworthy that even after the consensus meeting and with full access to MRs, the experts failed to agree on three cases. This highlights the fact that even in a multidisciplinary review, the atypical presentation of some geriatric patients creates indecision. A comparative analysis of clinical features for older patients with vs. without an indication for

antibiotic therapy might provide insights into these atypical presentations.

The distribution of infections in our study was in line with the literature data: the majority of the infections concerned the lungs and the urinary tracts [27, 30]. However, the prevalence of viral co-infection in our 55 patients with bacterial lung infections (14.5%) was lower than those reported by Das et al. (24.5%) and Burk et al. (31%) [26, 27]. This difference might be due to the fact that only 11 of these 55 patients were screened with PCR tests.

One of the strengths of our study was the consensus meeting to discuss discordant cases; this allowed the experts to harmonize their adjudications of on the primary endpoint in the most complex cases. During the meeting, the experts were easily able to review the indication or the lack of an indication for antibiotic therapy - especially when one of the three physicians had been unable to classify the case in question.

The limitations of our study were mostly related to the retrospective methodology; this might have led to information bias because our experts could not examine the included patients. The double chart review (individually and as a group) was very time consuming and might not be feasible in routine clinical practice. The good agreement observed in the present study was probably influenced by the fact that the experts had worked regularly together and might not be reproduced by a trio of experts in another hospital center.

Our results highlighted the complexity of decision-making for antibiotic therapy – even when all the data from the ED visit and the subsequent hospital stay are available. Although the initial level of agreement was substantial (according to Landis and Koch's guidelines), the level of inter-expert agreement appeared to depend on the physicians' medical specialties. Our application of a multidisciplinary method made it possible to resolve 52 initially discordant MRs with an indication for antibiotic therapy. This method might not be easily applicable in routine clinical practice. The complexity of the geriatric clinical presentation, especially for infections, would require the creation of multidisciplinary mobile teams (geriatrician, infectiologist) by the hospital administrators, to promote collaboration with the ED. These multidisciplinary teams will be able to help in the decision making of antibiotic therapy, with the emergency physicians, in the most complex geriatric cases, especially when there is a doubt about an infection (e.g. suspected lung infections).

5. Conclusion

This study is the first step towards better identification of atypical forms of bacterial infection in older people. The results of this novel study showed that a multidisciplinary review of older patients in the ED improved the identification of bacterial infections, with a substantial level of agreement between the three experts. However, the level of inter-expert agreement might have depended on the physicians' medical specialties. Further research on paraclinical factors (imaging, lab tests, etc.) and clinical factors associated with the diagnosis of a bacterial infection on arrival in the ED might help physicians to identify older patients with atypical clinical presentations more reliably.

Declarations

Author contribution statement

Matthieu Coulangeat: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Nathalie Polisset, Fanny Poitou, Adrien Lemaigen: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Emeline Laurent: Conceived and designed the experiments; Analyzed and interpreted the data.

Bertrand Fougère: Conceived and designed the experiments.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Appendix

Appendix 1. Landis and Koch scale.

Fleiss' kappa	Level of agreement
0.81–1.00	Almost perfect
0.61–0.80	Substantial
0.41–0.60	Moderate
0.21–0.40	Fair
0.00–0.20	Slight
< 0	None

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Additional information

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