Journal of Hospital Infection 90 (2015) 117–125

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Highlighting clinical needs in *Clostridium difficile* infection: the views of European healthcare professionals at the front line

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ARTICLE INFO

Article history:
Received 1 October 2014
Accepted 23 December 2014
Available online 11 March 2015

Keywords:
Clostridium difficile
Consensus opinion
Delphi method

SUMMARY

Background: *Clostridium difficile* infection (CDI) is the leading cause of infectious nosocomial diarrhoea in Europe. Despite increased focus, its incidence and severity are increasing in many European countries.

Aim: We developed a series of consensus statements to identify unmet clinical needs in the recognition and management of CDI.

Methods: A consortium of European experts prepared a series of 29 statements representing their collective views on the diagnosis and management of CDI in Europe. The statements were grouped into the following six broad themes: diagnosis; definitions of severity; treatment failure, recurrence and its consequences; infection prevention and control interventions; education and antimicrobial stewardship; and National CDI clinical guidance and policy. These statements were reviewed using questionnaires by 1047 clinicians involved in managing CDI, who indicated their level of agreement with each statement.

Findings: Levels of agreement exceeded the 66% threshold for consensus for 27 out of 29 statements (93.1%), indicating strong support. Variance between countries and specialties was analysed and showed strong alignment with the overall consensus scores.

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http://dx.doi.org/10.1016/j.jhin.2015.03.001

Conclusion: Based on the consensus scores of the respondent group, recommendations are suggested for the further development of CDI services in order to reduce transmission and recurrence and to ensure that appropriate diagnosis and treatment strategies are applied across all healthcare settings.

Introduction

Clostridium difficile is the leading cause of infectious nosocomial bacterial diarrhoea in industrialized countries.[1] The incidence and severity of *C. difficile* infection (CDI) is increasing in most countries and is associated with significant morbidity and mortality.[2] This represents a large clinical burden due to resultant severe diarrhoea and potential complications, including pseudomembranous colitis, toxic megacolon, colonic perforation and sepsis.[3,4] Recognized risk factors for disease include antimicrobial therapy, advanced age, treatment with proton pump inhibitors and immunological non-responsiveness to CDI.[5] From a patient perspective, CDI is associated with impaired quality of life.[6] In addition, there is an association with prolonged hospitalization and increased healthcare costs, making CDI an increasingly important public health issue.[6–11]

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has highlighted recurrence as the most important issue in the management of CDI.[12] Up to 25% of patients suffer a recurrence of infection within 30 days following treatment.[13–15] For patients who have already experienced one recurrence, the risk of further recurrence is estimated to be between 40% and 60%.[16,17] Recurrent CDI is a difficult-to-treat problem, with an impact on both length of stay and hospitalization costs, particularly in patients with immunosuppression, renal impairment or who are aged ≥65 years.[18–20] Reducing recurrences could potentially reduce the clinical burden, reduce the economic impact of treating additional episodes, and limit spread by onward transmission.

Although uncomplicated cases of CDI have traditionally been treated with metronidazole or oral vancomycin, recent reports suggest that CDI is becoming increasingly difficult to treat.[21–23] Patients with hospital-associated CDI have a 30-day attributable mortality between 3% and 30%.[15] Surgical therapies such as total colectomy are required in 3–5% of fulminant CDI cases and are associated with mortality rates ranging from 34% to 80%.[24–28] Many patients with CDI are already vulnerable due to comorbidities; hospitalized patients with CDI are up to three times more likely than those without CDI to die in hospital or within 30 days of admission.[12]

The clinical burden of managing primary cases and recurrences, together with associated management such as cleaning and decontamination, contribute to significant economic costs. US studies estimate the economic burden of CDI to vary between $2,450 and $40,000 per episode.[10] A substantial element of the additional cost relates to the accommodation costs resulting from a prolonged hospital stay. A systematic review of costs related to CDI in Europe found that incremental costs ranged from £4,577 in Ireland to £8,843 in Germany.[29] A German study showed a median cost of treating CDI of €33,840 per patient, an increase of €7,147 over non-infected matched control cases.[30] Overall the cost of CDI is estimated at €3 billion per year in the EU and there is concern that this will rise as the population aged >65 years increases.[2]

We sought to identify a set of consensus views representing a range of healthcare professionals across Europe. In particular, the attitudes and perceived unmet clinical needs regarding CDI were solicited. The process explored the reactions of a wide group of respondents to the consensus statements devised by this group, allowing comparison of attitudes and views from different national perspectives across Europe.

Methods

Astellas Pharma EMEA initiated and fully supported the consensus project including the selection of the initial faculty of experts, who were able to cover the broad aspects of CDI management. Astellas Pharma EMEA commissioned Triducive Ltd to facilitate the project and analyse the responses to the consensus statements, in line with the Delphi methodology. Astellas Pharma EMEA provided editorial assistance for the final manuscript by way of a factual accuracy check only. The author group, led by Dr S. Goldenberg, has jointly prepared the manuscript.

An international group of ten physicians including microbiologists, gastroenterologists, infectious diseases and intensive care physicians experienced in the management of CDI, were invited by Astellas Pharma EMEA to meet in Autumn 2013 with the objective of defining themes for future developments in the management of CDI. The ideas developed by the group were not restricted and the following broad themes emerged:

- Diagnosis of CDI
- Definitions of severity
- Treatment failure, recurrence and its consequences
- Infection prevention and control interventions across all care settings
- Education and antimicrobial stewardship
- National CDI clinical guidance and policy.

Discussion around each of these themes generated a set of 29 consensus statements. Whereas the group developed the initial consensus statements, the involvement of a wider audience reflecting the views of key stakeholders across Europe is essential in order to develop a robust consensus. Therefore, the statements were circulated by questionnaire across Europe in order to test levels of agreement. Questionnaires were sent to healthcare professionals across specialties reflecting the roles of the steering group. The questionnaires were circulated to personal contacts of the steering group, by contacts of Astellas sales representatives, through e-mail distribution lists of professional societies with an interest in

Table I
Respondent roles

Respondent specialty/professional group	*N* (%)
Intensive care	240 (22.9)
Infectious diseases	224 (21.4)
Internal medicine	164 (15.7)
Microbiology	117 (11.2)
Unknown role/anonymous	94 (9)
GI medicine/gastroenterology	87 (8.3)
Haematology/oncology	66 (6.3)
Geriatrics	19 (1.8)
Pharmacy	16 (1.5)
Transplant surgery	16 (1.5)
Palliative care	4 (0.4)
Total	1047

GI, gastrointestinal.

Table II
Respondents by country

Country	*N* (%)
Germany	427 (40.8)
Italy	166 (15.9)
Spain	137 (13.1)
Sweden	99 (9.4)
France	98 (9.4)
UK	64 (6.1)
Austria	38 (3.6)
Finland	18 (1.7)
Total	1047

infection and at infectious diseases medical conferences. In all countries except Spain, the questionnaires were written in English.

In order to achieve consensus with the wider group, a Delphi methodology was used.[31] The Delphi method works through written feedback, in order to measure consensus or agreement where differing opinions may exist. The level of individual agreement with each statement is measured using a four-point Likert scale, which allows respondents to record levels of agreement with each statement and suggest changes as appropriate. The four-point Likert scale forces either agreement or disagreement with each statement (strongly disagree, disagree, agree, or strongly agree).

Following review of the responses as numbers increased, the process allows the modification of each statement if necessary in order to increase the level of agreement and therefore represent the majority view of respondents.

Results

A total of 1047 respondents completed questionnaires within Europe, distributed across a variety of professional roles (Table I). The greatest number of respondents was from intensive care (22.9%, $N = 240$), followed by infectious diseases (21.4%, $N = 224$), internal medicine (15.7%, $N = 164$), and microbiology (11.2%, $N = 117$).

Respondents were distributed across Europe by country (Table II). The majority of respondents were from Germany (40.8%, $N = 427$), followed by Italy (15.9%, $N = 166$) and Spain (13.1%, $N = 137$).

The Consensus Group predefined the threshold of agreement for consensus to be $\geq$66%. Consensus was defined as 'high' at >66% and as 'very high' at >90%. Only two statements failed to meet this criterion: in all, 27 of the 29 statements (93.1%) achieved agreement scores of >66%. Statement 4 scored 65.2% and statement 12 scored 60.1% (Figure 1). In total, 20 of the statements achieved very high consensus, >90%. Individual scores for each statement are shown in Table III.

Although some variance was seen between different countries (Figure 2), the pattern of country responses is well aligned with the overall consensus scores. As with the overall analysis, statement 4 achieved the lowest levels of agreement in all countries, with statement 8 scoring low in Sweden, France, and the UK and statement 12 achieving lowest consensus in Sweden, Spain, France, and Germany. Statement 12 showed the greatest variance between countries as the UK score of 91.9% agreement is markedly different from that of other countries.

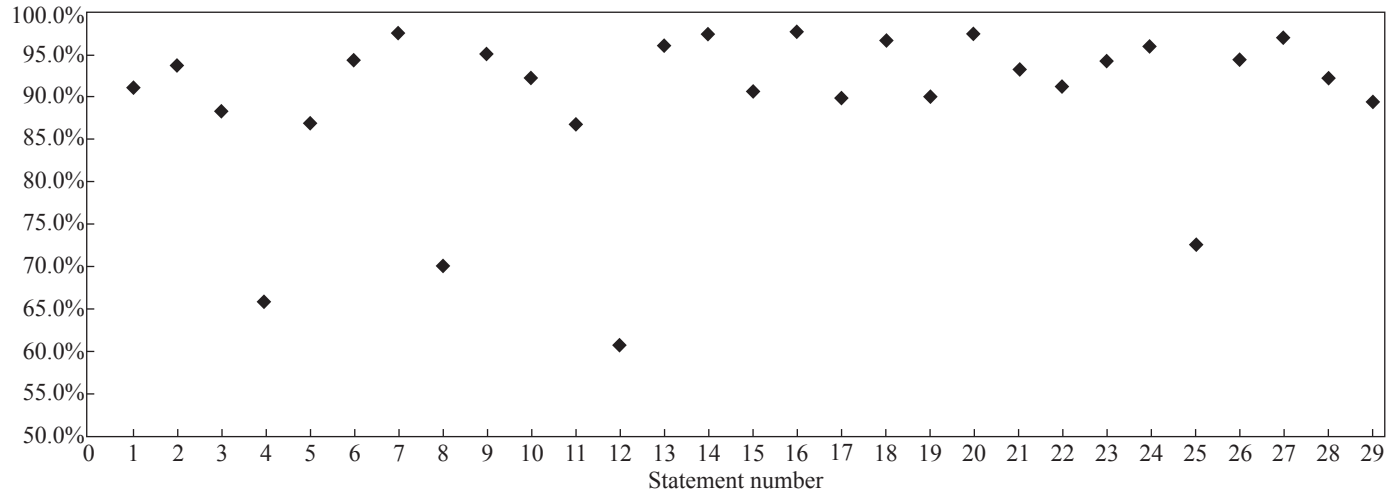

Figure 1. Total consensus agreement scores.

Table III
Individual agreement scores by statement

Theme		Statement	Overall agreement
Diagnosis of CDI (at-risk patient considerations)	1.	*Clostridium difficile* testing should be performed on all stools from patients presenting with healthcare-associated diarrhoea	91.0%
	2.	Clearly defined clinical algorithms should be implemented for stool specimen collection in all European countries	93.5%
	3.	The optimal method for laboratory diagnosis of CDI is a two-stage algorithm that incorporates a test for GDH (or a NAAT) followed by a toxin EIA	88.3%
	4.	The role of colonoscopy/sigmoidoscopy should be further defined as part of the diagnostic work-up for CDI	65.9%
Defining severe vs non-severe CDI	5.	Criteria for defining severity of CDI vary between existing guidelines and have not yet been fully characterized and validated	86.9%
	6.	CDI is a potentially life-threatening infection and therefore patients with severe CDI should be monitored intensively	94.2%
	7.	CDI treatment should be guided by diagnosis and by the patient's underlying condition and comorbidities	97.4%
	8.	Mortality rates do not correlate with the current definitions of severe vs non-severe CDI	70.1%
Guidance on how to respond to treatment failure and CDI recurrence	9.	A better understanding of the reasons for treatment failure is needed to improve CDI management	94.9%
	10.	More evidence is needed to inform treatment strategies for CDI treatment failure	92.1%
	11.	A validated measure of treatment responsiveness is required based on biomarkers/ clinical parameters	86.6%
	12.	For patients with severe CDI who are failing treatment; to reflect the decision-making process while a severely ill patient is on therapy and not responding, surgical treatment should be actively considered at an early stage	60.7%
Consequences of CDI recurrence	13.	Patients' underlying comorbidities are a predictor for increased mortality with CDI	96.1%
	14.	Recurrent CDI is a strong contributor to poor clinical outcomes, increased length of hospital stay and increased costs	97.3%
	15.	Treatment decisions for both initial infection and recurrent CDI should take into account the impact on resource utilization and wider societal costs	90.7%
	16.	There are certain patients, e.g. those receiving concomitant antibiotics, immunosuppressants, oncologic treatments, post surgery, who are at high risk of serious clinical consequences of recurrent CDI	97.5%
	17.	Awareness of the recurrent nature of CDI should be recognized and consistent long-term follow-up of CDI patients is desirable	89.8%

Infection control measures for CDI in care settings (cost and resource management)	18.	Infection control should be a priority at all levels of healthcare management, including facility design ensuring sufficient resources are made available for consistent and sufficient decontamination	96.5%
	19.	Awareness of the signs and symptoms of CDI need to be increased across all healthcare professionals to drive improved testing and diagnosis and all patients with diarrhoea should be treated with contact precautions until proven non-infectious	90.1%
	20	Improving compliance with appropriate infection control measures is crucial in preventing transmission of *C. difficile* including the practice of hand hygiene by healthcare professionals, patients, and relatives using soap and water	97.4%
	21.	Sufficient isolation facilities, meeting consistent defined standards, should be available for all patients with CDI or suspected CDI in all healthcare facilities	93.2%
Education and antibiotic stewardship	22.	Managers of all healthcare systems and institutions should assign a high priority to CDI to drive educational programmes targeting all healthcare practitioners	91.1%
	23.	Improved co-operation between hospitals, nursing homes and community healthcare is necessary to increase awareness of CDI and ultimately improve diagnosis, treatment and prevention	94.3%
	24.	Antibiotic stewardship needs to be implemented in all institutions to ensure effective use of antimicrobials and to educate healthcare professionals on the impact of antibiotic prescribing and the consequences of treating CDI	96.0%
	25.	Antibiotics should not be prescribed without the approval of a professional specifically trained in antimicrobial prescribing	72.6%
National CDI policy	26.	National policy for CDI should reflect the evidence base and offer a framework for implementation of national CDI guidelines at all levels of healthcare provision	94.4%
	27.	National CDI policy should aim to ensure consistent prevention, diagnosis and treatment of CDI in all healthcare settings	96.9%
	28.	Standardized and transparent reporting of CDI should be adopted nationally to ensure comparability of epidemiological data	92.2%
	29.	Europe-wide harmonization of CDI data collection and reporting is desirable	89.5%

CDI, *Clostridium difficile* infection; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; EIA, enzyme immunoassay.

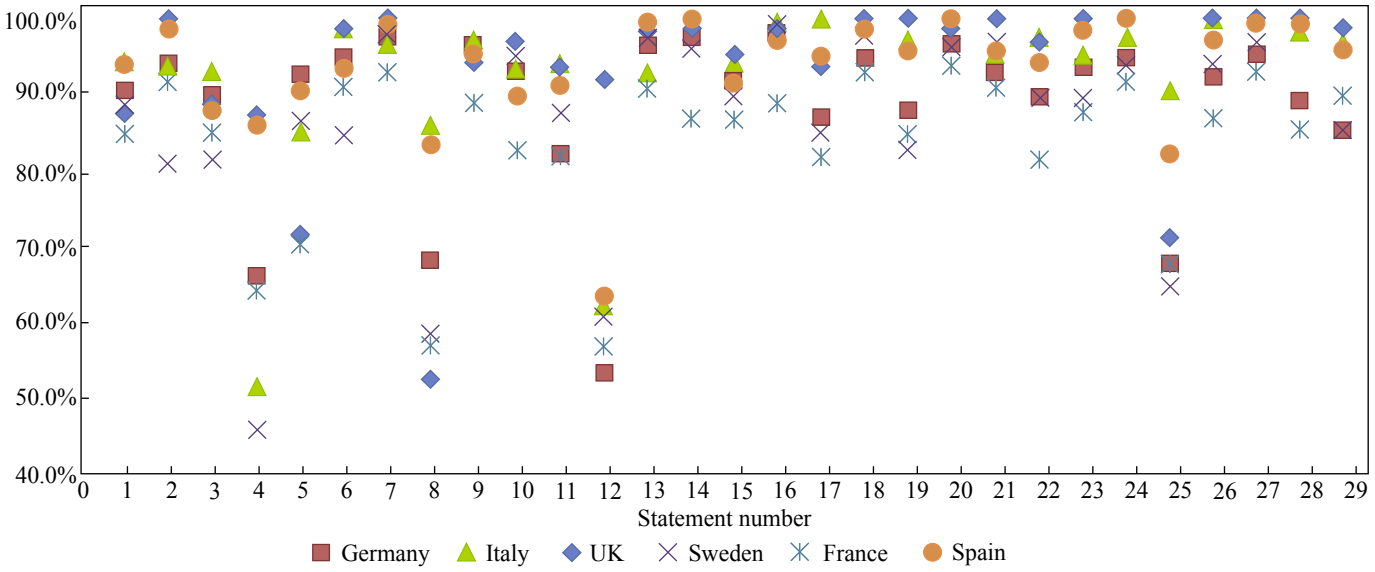

Figure 2. Consensus agreement scores by country.

The responses are also well aligned when analysed by specialty with internal medicine, yielding the lowest agreement scores and microbiology the highest (Figure 3).

Overall, high levels of agreement with 27 of the 29 statements suggest that consensus is strong, with little variation between countries or specialties.

Discussion

Diagnosis of CDI

Overall agreement with the statements concerning diagnosis of CDI is high (>66%) or very high (>90%) with the exception of statement 4 (65.9%). The same pattern is seen across countries and specialties. Respondents strongly agree that:

- *C. difficile* testing should be performed on all stools from patients presenting with healthcare-associated diarrhoea (91.0%);
- clearly defined clinical algorithms should be implemented for stool specimen collection in all European countries (93.5%);
- the optimal method for laboratory diagnosis of CDI is a two-stage algorithm that incorporates a test for glutamate dehydrogenase (or a nucleic acid amplification test) followed by a toxin enzyme immunoassay (88.3%).

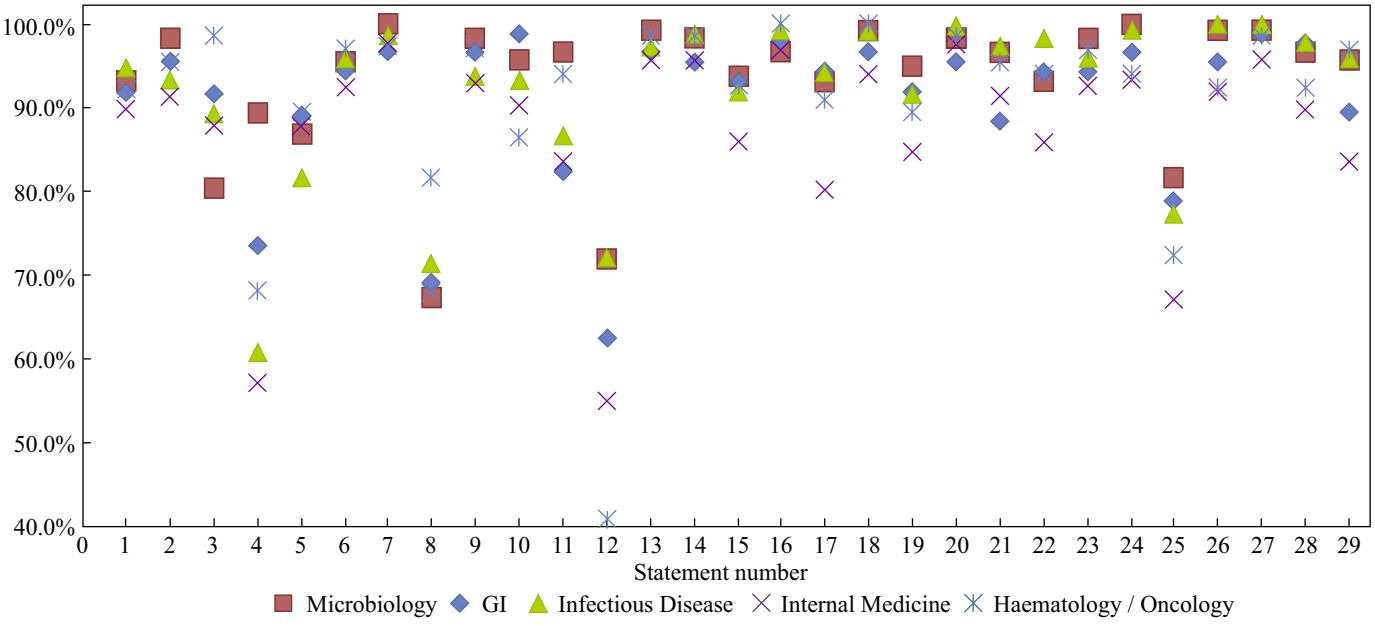

Figure 3. Consensus agreement scores by specialty.

Statement 4, concerning the role of colonoscopy and sigmoidoscopy within the diagnostic work-up, achieved the lowest score of all of the statements (65.9% agreement) and failed to meet the consensus threshold of >66%. Presumably, the phrasing of the statement is too ambiguous to give a conclusive response. Whereas it is clear that most respondents support further definition of the role of colonoscopy and sigmoidoscopy, the low agreement score may be due to concerns that the sensitivity of endoscopy is too low to implement into primary diagnostic algorithms for CDI.[32,33] However, in severely ill patients with acute onset of bloody diarrhoea, endoscopic visualization of the lower gastrointestinal tract may allow rapid exclusion of relevant differential diagnoses of CDI. Thus, a consensus needs to be reached about which patient groups may benefit from early endoscopy for suspected CDI.

Definitions of severity

All statements within this section achieved overall agreement scores of ≥70%. Further clarity may be needed to define the severity of CDI, aligned with mortality data so that appropriate treatment strategies can be applied. It should be noted that respondents in the UK, Sweden, and France showed lower agreement that mortality rates do not correlate with current definitions of CDI severity (statement 8), whereas respondents from Spain and Italy were more strongly supportive of this statement, which may reflect differing epidemiology. Overall consensus is supportive of these statements.

Treatment failure, recurrence and their consequences

Agreement with statements 9 and 10 exceeding 90% indicates a call from respondents for clarity regarding reasons for treatment failure and the definition of appropriate strategies for managing patients in whom treatment has failed. There is also strong support (86.3%) for a validated measure of treatment response.

Statement 12 achieved the lowest score overall (60.7%), suggesting that respondents are less supportive of considering surgery at an early stage. However, when examined by country, it is clear that respondents from the UK agreed more strongly than those from other countries. This may suggest that a lack of clarity in the wording of the statement contributed to lower levels of agreement or that the UK experiences more severe cases, with a need for surgical intervention. When examined by specialty, responses are more closely aligned.

Respondents also agreed that:

- patients' underlying comorbidities are a predictor for increased mortality with CDI (96.1%);
- recurrent CDI is a strong contributor to poor clinical outcomes, increased length of hospital stay and increased costs (97.3%);
- treatment decisions should take into account impacts on resource use and wider societal costs (90.7%);
- there are certain patients, e.g. those receiving concomitant antibiotics, immunosuppressants, oncologic treatments, post surgery, who are at high risk of serious clinical consequences of recurrent CDI (97.5%);
- awareness of the recurrent nature of CDI should be recognized and consistent long-term follow-up of CDI patients is desirable (89.8%).

Control of infection for CDI across care settings

High overall agreement scores >90% for all statements in this category reflect strong support for the need to prioritize infection control measures in all care settings. Respondents strongly agree that:

- infection control should be a priority at all levels of healthcare management, including facility design, to ensure that sufficient resources are made available for consistent and sufficient decontamination (96.5%);
- awareness of the signs and symptoms of CDI need to be increased across all healthcare professionals to drive improved testing and diagnosis and all patients with diarrhoea should be treated with contact precautions until proven non-infectious (90.1%);
- improving compliance with appropriate infection control measures is crucial in preventing transmission of *C. difficile*, including the practice of hand hygiene by healthcare professionals, patients, and relatives using soap and water (97.4%);
- sufficient isolation facilities that meet consistent defined standards should be available for all patients with CDI or suspected CDI in all healthcare facilities (93.2%).

Education and antibiotic stewardship

Strong overall support for statement 24 (96.0%) indicates that respondents agree with the need for antibiotic stewardship measures to be implemented in all institutions to ensure effective use of antimicrobials and to educate healthcare professionals on the impact of antibiotic prescribing and the consequences of treating CDI. Whereas consensus was clearly achieved for statement 25 (72.6%), it is clear that fewer respondents are comfortable with more direct control methods for the prescribing of antibiotics. This consensus is well aligned across specialties, but less so between countries.

Respondents from Italy and Spain were more accepting of antibiotic prescribing being limited to specifically trained professionals, than were those from Germany, the UK, Sweden, and France. This may be because of an increased awareness of the need to limit antibiotic prescribing in Italy and Spain following the recent ECDC report, which showed that Italy and Spain had the highest antimicrobial use of the countries observed.[34]

National CDI policy

All statements in this category achieved high levels of overall agreement (>89.4%) and were well aligned by country and specialty. Respondents strongly agreed that:

- national policy for CDI should reflect the evidence base and offer a framework for implementation of national CDI guidelines at all levels of healthcare (94.4%);

- national CDI policy should aim to ensure consistent prevention, diagnosis, and treatment of CDI in all healthcare settings (96.9%);
- standardized and transparent reporting of CDI should be adopted nationally to ensure comparability of epidemiological data (92.2%);
- Europe-wide harmonization of CDI data collection and reporting is desirable (89.5%).

There are several limitations to this study. First, the study captured the views of a limited group of specialists mostly within infectious diseases, microbiology, intensive care, and internal medicine. The methods employed to collect the data meant that there was a much stronger focus on these specialties and that other groups are under-represented (e.g. geriatrics) or omitted completely (e.g. general or gastrointestinal surgery). Similarly, the study focused on Western European countries only, so is not representative of opinions and practice of clinicians in Eastern Europe.

In conclusion, the high levels of consensus achieved from the 1047 respondents across eight European countries suggest that issues relating to the management of CDI are well understood by clinical professionals. These statements are offered as suggested standards, and those responsible for the management of hospital-acquired infection including CDI may find them useful in assessing their alignment with them. An understanding of the actual variance between these standards and common clinical practice may support further improvement of CDI treatment and the management of recurrent cases.

Additional research is required in a number of areas including parameters to differentiate between severe and mild CDI. In addition, clearer guidance regarding predictors for CDI and recurrence will assist in defining optimal case management approaches. Societal and community impacts of CDI are not well described and also require further investigation.

The role of surgery in managing severe CDI and the value of colonoscopy and sigmoidoscopy in diagnosis require clarification. The correlation between mortality rates and current definitions of severe and non-severe CDI is poorly defined and respondent attitudes show some variance across European countries. This may lead to inequity of care provision and effort should be made to encourage hospitals to report incidence data clearly and ensure that they are either reaching infection control targets or are on clear trajectory to achieving them.

This group offers the following recommendations for the future management of CDI:

1. Definitions for the severity of CDI need to be more robust. In particular, a meta-analysis of the literature is needed to identify definitions of severe and non-severe CDI. This will simplify and clarify appropriate reporting of cases.
2. Clearly defined clinical algorithms for stool specimen selection, collection, and testing should be implemented in all European countries.
3. We must better define how optimal CDI treatment can be planned for patients receiving concomitant antibiotics, immunosuppressants, oncologic treatments and those who have had recent surgery or have other risk factors such as PPI use.
4. Infection control interventions are critical in the management of CDI and they should be resourced appropriately and applied robustly to ensure that transmission of CDI is limited.
5. Hospitals and community-based health and social care services should collaborate to increase awareness of CDI and ultimately improve prevention, diagnosis and treatment.
6. Antibiotic stewardship should be improved in all healthcare institutions and should include education for all healthcare professionals, particularly in countries with recognized high use of antimicrobials.
7. National policies should seek to ensure consistent surveillance, prevention, diagnosis, and treatment of CDI in all healthcare settings.

In addition, it is hoped that this work will allow us to understand attitudes to guidance within Europe and provide a platform for the support of proactive management of CDI.

Funding and conflict of interest statement

Astellas Pharma EMEA initiated and fully supported the consensus project including the selection of the initial faculty of experts, who were able to cover the broad aspects of CDI management. Astellas Pharma EMEA paid the expert group an honorarium and travel expenses. Astellas Pharma EMEA commissioned Triducive Ltd to facilitate the project and analyse the responses to the consensus statements, in line with the Delphi methodology, and supported the authors in producing the manuscript. Astellas Pharma EMEA provided editorial assistance for the final manuscript by way of a factual accuracy check only. H. Seifert reports grants or research support from the Bundesministerium für Bildung und Forschung (BMBF), Germany, the German Center for Infection Research, Basilea, Novartis and Pfizer; has been a consultant for Astellas, AstraZeneca, Basilea, Cubist, Novartis, Pfizer, and The Medicines Company; and has received payments for lectures from MSD, Novartis, and Pfizer. A. Stallmach reports honoraria for participating in scientific advisory boards organized by Astellas. All of his activities and contracts are in conformity with the 'FSA-Kodex Fachkreise' (voluntary self-monitoring code for expert consultants to the pharmaceutical industry), have been checked by the Medicolegal Department of the University Hospital Jena, and have been approved by the directorate of the Faculty of Medicine. S. Goldenberg reports consulting fees, lecture fees, and research grants from Astellas. V. Anttila reports research support from MSD, Pfizer, GSK, and Astellas, consulting fees from MSD, and lecture fees from MSD, Pfizer, and Astellas. D. Jenkins reports speaker fees and advisory board fees from Astellas and is a director of Healthcare Infection Prevention Ltd. T. Galperine reports advisory board fees from Astellas. N. Petrosillo reports speaker's fees from MSD, Novartis, Astellas, Gilead, Pfizer, advisory board fees from Carefusion, Johnson & Johnson, Achaogen, and The Medicines Company. T. Norén reports advisory board fees from Astellas.

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